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Announcement

SOME months ago, Dr. Fred M. Smith announced that he would be unable to continue as Editor of the AMERICAN HEART JOURNAL after the end of 1945. His resignation came as a great surprise, but the Directors of the American Heart Association could not feel justified in asking the continuation of the labors that he has performed so well and faithfully for eight years and reluctantly agreed to select a successor.

Only editors themselves and those in close touch with their activities can realize the enormous amount of time and energy that must be given to the successful accomplishment of their duties. Even when full use is made of associate editors and members of the Editorial Board, most of the responsibility for the selection and editing of papers and the determination of editorial policies falls upon the Editor-in-Chief and the one Associate Editor who serves directly with him. That Dr. Smith has recognized and lived up to the responsibilities of his position, no one who knows the AMERICAN HEART JOURNAL would question. He has more than justified his appointment eight years ago, and has made a lasting contribution to the cause of better medicine and better medical literature in the United States. In this, the final issue of the JOURNAL under his Editorship, the Directors of the American Heart Association wish to express their deep gratitude for his unselfish devotion and unswerving loyalty, for the time and effort that he gave so generously, and for the intelligent direction that has kept the JOURNAL at such a high level of excellence.

To his chief associates also, the Directors wish to express their heartfelt appreciation. Their splendid work receives little notice or praise; it is largely taken for granted, but without it the JOURNAL would suffer greatly. Upon the able shoulders of Dr. Horace M. Korns fell a great deal of the responsibility for the editing and revision of manuscripts and for the final form in which papers were published. Dr. Smith and other associates have testified repeatedly to the unselfish manner in which he devoted himself to this work. He has left the University of Iowa Medical School to enter the practice of medicine, and the best wishes of his associates go with him.

Dr. Hugh McCulloch has been an Associate Editor of the JOURNAL since its founding in 1925. For some years he has also been in charge of the important Department of Abstracts and Reviews. For his long, faithful, and distinguished service this public acknowledgment and expression of gratitude are most inadequate repayment.

In accordance with the agreement relating to this matter, the Board of Directors of the American Heart Association selected a new Editor-in-Chief, subject to the approval of The C. V. Mosby Company. Their selection was Dr. Thomas M. McMillan, of Philadelphia, who was accepted with enthusiasm

by the publishers. Immediately upon his confirmation, Dr. McMillan departed for conferences with the president and the staff of the Mosby Company and with Dr. Smith.

The Directors of the Association, regretful at the resignation of Dr. Smith, feel a great sense of relief and security in the knowledge that Dr. McMillan is to succeed him. Known in this country and abroad as a distinguished specialist in the field of diseases of the heart, he brings to his new position authority and prestige. Those who know him well realize that he has an unusual combination of qualities that would seem to fit him ideally for his new responsibilities. In addition to the unusual charm and graciousness which have endeared him to all his associates, he has keen critical ability, an extensive knowledge of medical literature, and a great fund of clinical experience and practical knowledge. He has accepted his new assignment with ardent enthusiasm and with an earnest desire to make the AMERICAN HEART JOURNAL one of the great medical journals of our time. It is with pride and complete confidence that the Directors of the Association present him to all readers of the JOURNAL and ask their full cooperation in the attempt to realize this laudable aim.

To Dr. Smith and his associate editors we say a reluctant farewell and extend our best wishes for continued success in their special work. To Dr. McMillan and the Editorial Board that he is now selecting we extend a most cordial welcome and promise full support in the months and years that lie ahead.

This announcement, properly devoted primarily to the departing and arriving editors, would be incomplete without a special word of thanks to The C. V. Mosby Co. and those members of their staff who are chiefly responsible for the publication of this JOURNAL. Both Dr. Smith and Dr. McMillan have spoken with warm appreciation of the cordiality and responsive cooperation of the publishers, and we have every confidence in their continued efforts to make the JOURNAL even finer.

H. M. MARVIN, M.D.
For the Board of Directors
American Heart Association

Original Communications

THE EFFECT OF SMOKING CIGARETTES ON THE PERIPHERAL BLOOD FLOW IN SUBJECTS IN THE OLDER AGE GROUP WITH CORONARY ARTERIOSCLEROSIS AND HYPERTENSION

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THE effect of the smoking of tobacco on the circulation has been the subject of many investigations. Its effects on the peripheral vascular system have taken on especial interest with the concern in the last few years about peripheral vascular diseases. In 1943, Evans and Stewart[1] reported observations upon the effect of the smoking of cigarettes on the peripheral blood flow in a group of young persons from 19 to 36 years of age. They found that smoking decreased the peripheral blood flow and increased the blood pressure and heart rate in these subjects. Similar effects were observed following the smoking of denicotinized cigarettes and those made of corn silk. It was suggested that these effects might be due to the effect of smoke on the respiratory tract. The literature bearing upon this subject was reviewed at that time. At the time this paper was written, a report by Goetz[2] which had been published two months earlier was not available to us. Goetz also found decrease in peripheral blood flow, as measured by digital volume, and attributed the effect also to "reflexes set in train by the irritation of smoke on the mucosa of the respiratory tract."

Since then, another excellent study of the effect on the circulation of smoking cigarettes and intravenously administering nicotine has been made by Roth, McDonald, and Sheard.[3] They found the effects of smoking cigarettes similar to those which we recorded, in the measurements which they made which could be compared with our results, but did not observe the effects following the smoking of corn silk. Their experiments are not strictly comparable to ours because of different objectives and different techniques. We were interested in the average effect of smoking on the average peripheral blood flow; therefore, we recorded temperatures from eleven areas on the body surface. They were interested in the temperature of a finger and a toe as samples of the skin temperature and as an index of peripheral vascular constriction. They were of the opinion that the effects they observed were to be attributed to nicotine. These recent observations of Evans and Stewart,[1] Goetz,[2] and Roth, McDonald, and Sheard[3] are all in agreement, however, about the general effects observed following the smoking of cigarettes.

Our earlier observations[1] were made on individuals in the younger age group, as were those of Roth, McDonald, and Sheard.[2] It seemed important to observe the effect of smoking on the peripheral blood flow in patients in the older age group, who were known to have vascular disease. Such observations

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form the subject of this paper. Patients were accordingly selected who were in the older age groups and who had known arterial disease: coronary artery disease, histories of coronary occlusion, hypertension, or arteriosclerosis. These patients showed no clinical evidence of peripheral vascular disease at the time these observations were made. In L. M., arteriosclerotic gangrene of the right foot required amputation forty-one days before these studies were made. The peripheral pulses were good in the left leg, and the skin temperatures of this extremity were warm. In the study reported here all the subjects smoked one brand of regular (standard) cigarettes. Studies were made of seventeen men, ranging in age from 38 to 81 years.

METHOD

The measurements of peripheral blood flow were made by means of a modification[4] of the method of Hardy and Soderstrom.[5] These observers have shown that, at temperatures below 28° C., the skin functions like a dead insulator when the subject is lying nude in the basal state, and that blood flow to the skin, thermal conductivity of the peripheral tissues, and vaporization are constant and minimum. With an increase in blood flow to the periphery, more heat is brought from the deeper tissues to the surface; this increases the thermal conductance of the superficial tissues, and, therefore, changes in thermal conductance become an index to peripheral blood flow. With this method, blood flow is expressed as a function of heat loss, surface area, *average skin temperature,* and rectal temperature. The method requires the recording of skin and rectal temperatures at known intervals, and of oxygen consumption, height, and body weight. The skin temperatures were recorded with a Hardy-Soderstrom radiometer from eleven points on the anterior surface of the body. The eleven areas were as follows: (1) forehead, (2) upper part of right side of chest, (3) lower part of left side of chest, (4) right side of abdomen, approximately at level of the umbilicus, (5) left arm, (6) left forearm, (7) dorsum of left hand, (8) upper part of right thigh, (9) lower part of right thigh, (10) leg, and (11) dorsum of left foot. This method measures the total amount of blood allotted to the periphery of the whole body, from the skin inward, for a depth of about 1 centimeter. It differs in this respect from those methods which measure the amount of blood flow going to a leg, arm, or finger. It is not possible to measure the amount of blood allotted to individual parts by this technique, but inferences can be made about this from the local skin temperatures. The resulting blood flow by this method is expressed in cubic centimeters per square meter of body surface. In addition to measurements relating to blood flow, the blood pressures and pulse rates were recorded between temperature readings.

PLAN OF PROCEDURE

The plan of procedure was essentially the same as that described in a recent publication.[4] In the present study, measurements of skin and rectal temperatures were made at ten-minute intervals, instead of at twenty-minute intervals as in previous work. Each set of measurements covered approximately ninety minutes. The measurements of blood pressure and pulse rate were recorded during free intervals between temperature readings. The basal metabolic rate was measured before smoking, immediately after smoking, and again at the end of a morning's observations. For the period before smoking, the first value for basal metabolic rate was used in the calculation of peripheral blood flow. For the period during smoking, the average of the oxygen consumption before, and immediately after, smoking was used for calculating peripheral blood flow. For

the phase after smoking, the difference between the oxygen consumption immediately after smoking and that at the conclusion of the experiment was divided by the number of periods of peripheral blood flow measurements in such a way that it was properly apportioned among these periods. All except two patients (D. G. and C. T.) were smokers, and all inhaled while smoking. The subjects smoked, in succession, two-thirds of two cigarettes at their normal inhalation depth and frequency; exaggerated smoking was avoided. The duration of smoking varied with the subjects from sixteen to eighteen minutes. A room temperature of 27° C., with a relative humidity of approximately 45 to 50 per cent, was maintained. The cigarettes were of the same brand for all subjects. They were purchased on the open market.

Four sets of observations were made before smoking in all except one patient (A. K.), from whom three calculations of peripheral blood flow could be made. One or two sets of observations were made during smoking from which two or three calculations, respectively, of peripheral blood flow could be made which were influenced by smoking. Four or five sets of observations were made after the subject had stopped smoking, from which three or four calculations, respectively, of peripheral blood flow could be made. The measurements made before, during, and after smoking were each averaged and indicated by "before," "during," and "after" in Table I.

All observations were made in the morning before breakfast with the subjects in a basal metabolic state. After the constant temperature room had been brought to 27° C. and around 45 per cent humidity, the patient lay on the bed, nude, covered with a sheet for one hour, for the body to adjust to this temperature. A room temperature of 27° C. was selected to be certain that vasodilatation was present and available for constriction to take place later during smoking, and also in order to make the observations comparable to the ones on the younger individuals.

RESULTS

The data relating to M. K. (Fig. 1), 67 years of age, who had arteriosclerotic heart disease, coronary sclerosis, and enlargement of the heart, serve to illustrate the effects of smoking. The data for all subjects are summarized in Table I.

Effect of Smoking on Peripheral Blood Flow.—The peripheral blood flow decreased during smoking* in thirteen patients and increased* in four (Fig. 1, Table I). In those in whom the peripheral blood flow decreased while smoking, the peripheral blood flow continued to fall in the period after smoking, or began to return toward or to the control level. The four subjects in whom the average peripheral blood flow for the smoking period was increased showed, nevertheless, during smoking or in the period after smoking, single observations in which the peripheral blood flow was greatly decreased.

For this group of thirteen patients, showing decrease in peripheral blood flow during smoking, the average peripheral blood flow before smoking was 78 c.c. per square meter of body surface per minute; during smoking, 48 c.c. per square meter of body surface per minute; and after smoking, 59 c.c. per square meter of body surface per minute. For the four showing increase in peripheral blood flow, the average before smoking was 50 c.c. per square meter of body surface per minute; during smoking, 68 c.c. per square meter of body surface per minute; and after smoking, 89 c.c. per square meter of body surface per minute.

*These groups are designated the "decreased peripheral blood flow group" and the "increased peripheral blood flow group" in the rest of the paper.

The Effect of Smoking on Blood Pressure.—The systolic blood pressure rose in eleven instances in which the peripheral blood flow was decreased, and was unchanged in three patients, while the diastolic blood pressure rose in every instance. The average for the group showed a blood pressure of 134/79 before, 145/86 during, and 143/83 after smoking. In the four patients in whom the peripheral blood flow increased on smoking, the blood pressure did not show any significant change as the result of smoking, being 160/89 before, 161/93 during, and 160/90 after smoking (Table I).

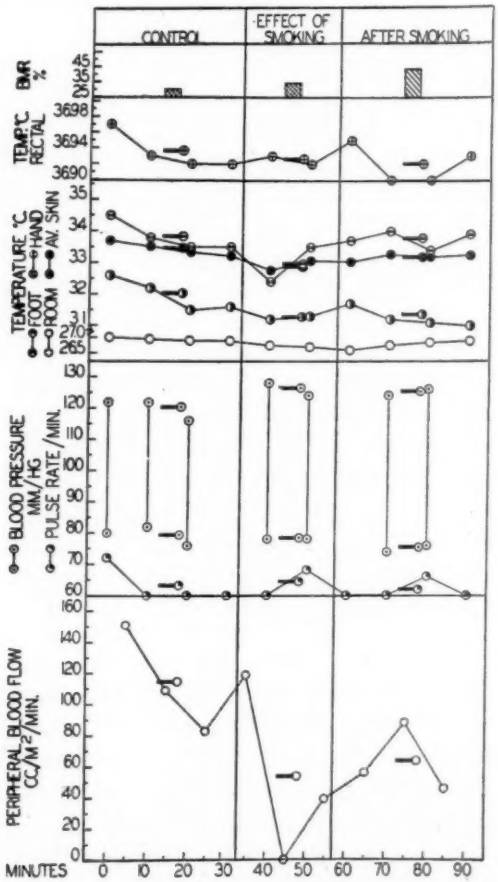

Fig. 1.—In this figure are shown the effects of smoking cigarettes on peripheral blood flow, average skin temperature, rectal temperature, temperatures of the hands and feet, pulse rate, blood pressure, and basal metabolic rate in M. K., 67 years of age, who had arteriosclerotic heart disease, coronary artery disease, and enlargement of the heart. All of the measurements of the peripheral blood flow, temperatures, etc., are recorded in the figure. The averages for each of the periods, namely, before, during, and after smoking, are indicated by solid bars with the appropriate symbols. The peripheral blood flow undergoes fluctuations from one ten-minute interval to the next as has already been described by Stewart and Evans.[1]

The Effect of Smoking on the Pulse Rate.—The pulse rate increased in eight patients and was unchanged in five in the group showing decrease in peripheral blood flow as the result of smoking; the averages for the whole group were 68 per minute before, 74 per minute during, and 72 per minute after smoking. Of the four showing increase in peripheral blood flow when smoking, two had slight increases in rate and two were unchanged; the averages for the whole group were 63 per minute before, 68 per minute during, and 64 per minute after smoking (Table I).

The Effect of Smoking on Basal Metabolic Rate.—There were no significant changes in basal metabolic rate as a result of smoking. In the decreased

peripheral blood flow group the averages were +12 per cent before, +12 per cent during, and +13 per cent after smoking, although there were changes in individual patients. The averages for the increased peripheral blood flow group were 6 per cent before, 11 per cent during, and 11 per cent after smoking (Table I).

The Effect of Smoking on Average Skin Temperature.—In the group showing decrease in peripheral blood flow when smoking, the average skin temperature decreased in nine patients either during or after smoking and increased in four. The average for the group was 33.88° C. before, 33.81° C. during, and 34.19° C. after smoking. The averages for those showing increase in peripheral blood flow showed essentially the same trends, being 34.23° C. before, 34.12° C. during, and 34.28° C. after. The average skin temperatures of these patients were higher than in the other group. The average maximum fall in temperature of the hand after smoking was 0.20° C., both in the decreased and increased peripheral blood flow groups, and in the feet the average maximum change was 0.10° C. increase in the increased peripheral blood flow group and 0.40° C. decrease in the decreased peripheral blood flow group. There were wide fluctuations in the temperatures of the hands and feet (Table I). The hands and feet exhibited the most marked changes, and the other areas of the body did not show any significant trends in the changes which were observed.

Effect of Smoking on Rectal Temperatures.—In the decreased peripheral blood flow group the rectal temperature increased in nine patients as a result of smoking, was unchanged in three, and decreased slightly in one. The average for the group was 37.03° C. before, 37.06° C. during, and 37.10° C. after smoking. The rectal temperatures increased in all of the four patients showing increase in peripheral blood flow when smoking; the average was 37.15° C. before 37.21° C. during, and 37.19° C. after smoking (Table I).

DISCUSSION

The peripheral blood flow decreased, as a result of smoking regular cigarettes, in thirteen patients and increased in four patients. In these latter four patients, however, the peripheral blood flow decreased in one or more of the values recorded either during or after smoking. The patients participating in this study were all in the later decades of life, had evidence of vascular disease, and were those in whom the vascular system may presumably have lost some of its resilience. In some instances the maximum fall in peripheral blood flow was attained while smoking and in others it was lowest in the period after the subject stopped smoking. In the subjects in the younger age group studied by Evans and Stewart,[1] there were six subjects in whom the peripheral blood flow decreased during the smoking of standard cigarettes in a manner comparable to the thirteen subjects in the observations now being reported (Table I). The averages for this normal group were 88 c.c. per square meter of body surface per minute before, 50 c.c. per square meter of body surface per minute during, and 60 c.c. per square meter of body surface per minute after smoking. The percentage changes as a result of smoking were, therefore, slightly greater in the normal group (the average decrease occasioned by smoking was 38 per cent in the older decades and 43 per cent in the younger decades) and the average return to the control levels took place more slowly in the younger age group.

In this older age group, the decrease in peripheral blood flow was accompanied by a slight rise in rectal temperature and by a slight fall in skin tem-

TABLE I. EFFECT OF SMOKING CIGARETTES ON THE PERIPHERAL BLOOD FLOW, RECTAL AND SKIN TEMPERATURES, HEART RATE, AND BLOOD PRESSURE

CASE AGE (YRS.) HISTORY NO.	TIME WITH REFERENCE TO SMOKING	PERIPHERAL BLOOD FLOW (C.C./M.²/MIN.)	AVERAGE RECTAL TEMPERATURE ° C.	AVERAGE WEIGHTED SKIN TEMPERATURE ° C.	SKIN TEMPERATURES AT ELEVEN POINTS ON THE BODY SURFACE											BLOOD PRESSURE MM. HG	PULSE RATE PER MIN.	BASAL METABOLIC RATE PER CENT	DIAGNOSIS
					1 ° C.	2 ° C.	3 ° C.	4 ° C.	5 ° C.	6 ° C.	7 ° C.	8 ° C.	9 ° C.	10 ° C.	11 ° C.				
Those in Whom Smoking Decreased the Peripheral Blood Flow																			
N. H.	Before	53	37.58	34.16	35.3	34.9	34.4	34.2	34.4	34.7	35.2	33.8	32.9	33.3	33.6	107/65	75	- 8	Arteriosclerotic heart
53	During	13	37.60	34.40	35.6	35.2	34.8	34.8	34.5	34.4	35.0	34.6	33.0	33.3	33.6	118/80	93	+ 4	disease. Angina pec-
275880	After	52	37.74	34.32	35.4	35.2	34.9	34.9	35.0	34.4	34.6	34.6	33.3	32.7	32.7	111/69	85	+ 6	toris. Anemia
D. G.	Before	81	36.89	34.19	35.1	34.7	34.3	34.6	33.9	33.7	34.4	34.3	33.2	33.7	34.3	115/75	65	- 9	Arteriosclerotic heart
63	During	47	36.94	34.22	35.1	34.5	34.3	34.6	33.9	33.9	34.6	34.3	33.2	33.8	35.5	118/80	72	- 9	disease. Coronary
83994	After	56	36.99	34.43	35.1	34.6	34.5	34.9	34.5	34.2	34.1	34.5	33.5	33.9	34.6	116/76	66	- 9	thrombosis
M. K.	Before	114	36.94	33.44	34.7	34.7	33.7	33.8	33.8	33.8	33.8	32.3	32.4	32.1	32.0	120/79	63	+30	Arteriosclerotic heart
67	During	53	36.93	32.92	34.3	34.3	33.4	33.5	33.6	33.0	33.0	33.0	31.8	31.4	31.3	126/78	64	+34	disease. Coronary ar-
352240	After	63	36.92	33.18	34.6	34.4	33.9	33.8	33.8	33.6	33.8	33.2	31.8	31.5	31.3	125/75	62	+43	tery disease. En-
																			larged heart
N. M.	Before	166	37.18	34.45	35.7	35.3	35.1	35.4	34.5	34.6	35.3	34.3	33.8	32.7	32.4	108/68	70	+37	History of fluctuation
38	During	136	37.28	34.34	35.7	35.5	34.8	35.1	34.7	34.6	34.3	34.4	33.7	32.6	32.6	118/74	84	+36	in blood pressure and
357527	After	130	37.29	34.39	35.6	35.5	34.7	35.2	34.6	34.6	34.8	34.9	33.6	32.7	32.3	127/81	84	+36	being high in last
																			two years
F. S.	Before	56	37.32	34.54	35.5	35.6	35.3	35.2	34.9	34.3	34.9	34.5	32.4	33.6	34.0	148/90	72	- 5	Hypertensive heart dis-
54	During	36	37.35	34.51	35.5	35.6	35.3	35.3	34.6	34.3	35.0	34.3	32.8	33.5	33.9	155/94	76	- 5	ease. Angina pec-
342341	After	16	37.39	34.71	35.5	35.5	35.6	35.3	34.9	34.7	34.8	34.6	33.1	33.5	34.2	153/100	74	- 5	toris. Auricular
																			fibrillation
F. C.	Before	79	36.78	34.10	34.4	34.7	34.3	34.0	34.2	33.7	34.8	33.7	33.9	33.1	35.1	152/98	73	+10	Hypertensive heart dis-
54	During	53	36.92	34.06	34.5	34.9	34.1	33.9	33.9	34.0	34.6	33.7	34.1	32.9	34.9	166/106	72	+11	ease. Enlarged
106423	After	95	36.96	33.95	34.3	34.3	34.0	33.7	33.9	33.9	34.4	33.4	34.1	33.1	35.1	156/106	74	+11	heart. Cerebral
																			thrombosis. Arterio-
																			sclerosis
P. L.	Before	79	37.40	33.71	34.0	34.8	33.8	34.6	33.7	33.0	34.5	33.2	33.1	32.3	34.1	197/103	83	+20	Hypertensive heart dis-
53	During	32	37.36	33.76	34.1	34.9	34.0	34.7	33.8	33.1	34.8	32.5	33.0	32.3	34.4	210/110	82	+19	ease. Coronary ar-
384879	After	71	37.39	33.89	34.1	35.0	34.3	34.7	34.0	33.1	34.8	32.7	33.2	32.5	34.5	208/106	81	+21	tery disease. Chronic
																			pyelonephritis
H. S.	Before	87	37.30	33.80	35.1	35.4	34.8	34.9	34.3	33.4	34.2	33.1	33.0	31.8	31.4	176/87	72	+36	Hypertension. Arterio-
77	During	22	37.38	33.34	35.1	35.2	34.2	34.4	34.1	34.4	33.9	32.4	32.4	30.9	30.9	172/94	76	+30	sclerotic heart dis-
109660	After	39	37.42	33.70	35.2	35.4	34.6	34.8	34.2	33.8	34.3	33.1	33.2	31.0	31.4	176/90	73	+32	ease. Auricular
																			fibrillation

H. S.	Before	84	36.40	33.48	34.6	34.0	33.4	33.4	33.2	32.9	34.5	32.4	33.3	32.9	33.8	107/64	62	- 0.4	Arteriosclerotic heart
70	During	59	36.41	33.73	34.4	34.5	33.9	33.6	33.4	33.4	35.0	32.8	33.4	33.1	34.5	115/70	68	- 0.4	disease. Coronary
61672	After	62	36.41	33.62	34.6	34.4	33.9	33.6	33.3	33.3	34.4	32.4	33.4	32.9	33.9	114/68	66	- 2	artery disease. Angina pectoris. Enlarged heart
A. K.	Before	62	36.70	33.79	34.4	34.3	33.9	34.2	33.4	33.3	34.8	34.0	32.8	32.9	33.8	127/61	56	+ 4	Arteriosclerotic heart
81	During	42	36.74	33.74	34.6	34.4	33.8	33.8	33.2	33.4	34.9	33.4	32.7	33.1	34.0	130/78	56	+ 3	disease. Coronary
230574	After	26	36.80	33.75	34.5	34.1	34.0	34.2	33.1	33.3	35.1	33.7	32.5	33.0	34.1	132/67	57	- 0.9	thrombosis. Generalized arteriosclerosis
V. B.	Before	49	36.89	33.43	33.8	34.3	34.1	33.6	34.4	33.5	34.4	32.6	32.8	31.3	33.1	108/68	53	- 7	Arteriosclerotic heart
54	During	35	36.88	33.28	34.7	34.9	34.1	34.4	34.0	33.9	33.8	32.8	32.3	30.6	32.6	112/75	58	- 8	disease. Coronary
364494	After	28	36.88	33.40	34.8	34.8	34.0	33.8	34.2	33.4	34.3	32.8	32.6	30.0	32.4	110/71	59	- 8	thrombosis
W. M.	Before	57	36.82	33.83	35.2	33.3	34.5	34.2	33.8	33.6	34.1	33.5	33.5	33.0	32.0	168/100	70	+15	Hypertensive and ar-
69	During	53	36.88	33.77	35.1	34.6	34.3	34.1	33.8	33.6	33.8	33.4	33.6	32.9	32.2	194/104	76	+12	teriosclerotic heart
212967	After	75	36.88	34.00	35.2	34.8	34.5	34.3	33.9	34.0	34.3	33.4	33.7	33.0	32.1	185/104	74	+13	disease. Enlarged heart. Coronary artery disease
L. M.	Before	46	37.13	33.60	34.7	34.8	33.4	34.9	33.6	33.2	35.0	32.4	34.1	31.6	32.1	132/70	71	+36	Arteriosclerotic gan-
65	During	37	37.13	33.52	34.8	34.7	33.4	34.9	33.7	33.4	35.0	32.3	34.3	31.4	31.9	146/70	80	+33	grene of the right
255998	After	51	37.17	33.65	34.9	35.1	33.9	35.0	33.9	33.5	34.9	32.4	34.0	31.2	32.1	144/72	80	+33	foot. Experiment 41 days after amputation
Averages	Before	78	37.03	33.88	34.8	34.7	34.2	34.4	34.0	33.7	34.6	33.5	32.9	32.6	33.2	134/79	68	+12	
	During	48	37.06	33.81	34.9	34.9	34.2	34.4	33.9	33.8	34.4	33.4	32.9	32.4	33.3	145/86	74	+12	
	After	59	37.10	34.19	34.9	34.9	34.4	34.5	34.1	33.8	34.5	33.5	33.0	32.4	33.1	143/83	72	+13	
Those in Whom Smoking Increased the Peripheral Blood Flow																			
B. C.	Before	91	37.01	34.35	35.0	35.0	34.9	35.4	34.5	34.0	34.4	34.8	33.5	33.2	32.8	163/91	74	+23	Hypertension. Arterio-
69	During	102	37.02	34.30	35.1	35.0	35.3	35.6	34.4	33.6	34.3	34.6	33.4	33.1	32.1	170/90	72	+27	sclerotic heart dis-
377456	After	124	37.09	34.42	35.1	35.1	35.4	35.7	34.4	34.0	34.5	34.5	33.5	33.3	32.4	163/91	76	+25	ease
J. S.	Before	39	36.91	34.12	35.0	34.7	34.3	34.7	34.4	34.7	35.0	33.7	33.6	32.7	33.5	149/75	55	- 1	Arteriosclerotic heart
52	During	51	37.01	34.14	35.3	34.8	34.5	34.9	34.5	34.6	34.9	33.5	33.7	32.5	33.4	150/78	60	+ 7	disease. Enlarged
158786	After	37	37.06	34.24	35.2	35.2	34.7	34.8	34.6	34.6	34.9	33.2	33.6	32.6	33.8	149/76	59	+ 5	heart
J. S.	Before	21	37.46	33.86	35.0	34.4	34.2	34.4	34.0	33.9	34.8	33.5	32.6	32.6	33.4	211/126	62	+ 4	Hypertensive heart dis-
44	During	37	37.49	33.79	35.3	34.6	34.4	34.2	34.2	34.0	34.6	33.2	32.4	32.6	33.0	212/122	78	+ 4	ease. Coronary
353263	After	136	37.29	34.04	35.0	34.6	34.8	34.5	34.2	34.1	35.0	33.4	32.6	32.8	33.9	204/124	66	+ 7	thrombosis

TABLE I—CONT'D

CASE AGE (YRS.) HISTORY NO.	TIME WITH REFERENCE TO SMOKING	PERIPHERAL BLOOD FLOW (C.C./M.²/MIN.)	AVERAGE RECTAL TEMPERATURE ° C.	AVERAGE WEIGHTED SKIN TEMPERATURE ° C.	SKIN TEMPERATURES AT ELEVEN POINTS ON THE BODY SURFACE											BLOOD PRESSURE MM. HG	PULSE RATE PER MIN.	BASAL METABOLIC RATE PER CENT	DIAGNOSIS
					1 ° C.	2 ° C.	3 ° C.	4 ° C.	5 ° C.	6 ° C.	7 ° C.	8 ° C.	9 ° C.	10 ° C.	11 ° C.				
C. T.	Before	47	37.20	34.60	35.2	35.0	34.8	35.2	34.7	34.0	34.7	34.6	34.5	33.8	33.9	115/64	60	- 4	Arteriosclerotic heart disease. Enlarged heart. Auricular fibrillation. Pulmonary fibrosis
52	During	82	37.32	34.24	35.4	35.1	34.5	34.3	34.7	34.1	34.1	34.5	34.0	32.9	33.5	110/80	60	+ 5	
355770	After	59	37.30	34.40	35.1	34.9	34.8	34.9	34.6	34.0	34.5	34.6	34.2	33.1	33.6	123/70	56	+ 6	
Averages	Before	50	37.15	34.23	35.1	34.8	34.6	34.9	34.4	34.2	34.7	34.2	33.6	33.1	33.4	160/89	63	+ 6	
	During	68	37.21	34.12	35.3	34.9	34.7	34.8	34.5	34.1	34.5	34.0	33.4	32.8	33.0	161/93	68	+11	
	After	89	37.19	34.28	35.1	35.0	34.9	35.0	34.5	34.2	34.7	33.9	33.5	33.0	33.4	160/90	64	+11	
Normal Subjects in Whom Smoking Decreased the Peripheral Blood Flow																			
F. H.	Before	77	36.78	33.87	34.2	34.0	34.0	34.1	34.1	33.9	34.6	33.6	33.7	33.3	33.5	112/67	56	- 3	
28	During	44	36.84	33.74	34.5	34.0	34.2	34.1	34.1	33.7	34.2	33.3	33.4	33.0	32.7	119/82	77	- 6	
69145	After	25	36.94	33.51	34.4	33.9	34.2	33.6	34.1	33.7	34.4	32.9	33.2	32.5	32.4	120/80	63	- 7	
R. B.	Before	39	37.10	33.41	34.9	34.2	34.4	34.7	33.7	33.7	33.8	33.9	33.0	33.2	26.3	105/69	60	+ 1	
26	During	10	37.14	33.79	34.8	34.8	35.1	35.2	34.3	34.1	34.1	34.1	34.3	33.5	25.2	122/81	86	0	
242245	After	52	37.11	33.71	34.8	34.6	34.7	34.9	34.0	34.1	34.2	34.2	33.8	33.5	25.7	117/77	76	0	
R. T.	Before	60	36.58	33.70	34.2	33.9	33.7	33.6	33.7	33.7	34.7	32.6	33.5	33.6	34.2	114/73	65	-19	
28	During	39	36.59	33.60	34.4	33.9	34.1	33.9	33.8	33.5	33.8	33.1	33.8	33.5	31.0	126/86	98	-15	
64949	After	65	36.53	33.64	34.3	33.9	34.0	33.8	33.6	33.7	34.3	33.1	33.8	33.4	31.6	120/79	72	-13	
W. B.	Before	71	36.95	34.18	34.7	35.4	35.1	35.1	34.0	33.5	34.7	33.8	33.2	34.0	30.6	97/65	64	- 1	
30	During	21	37.17	34.47	34.6	35.2	35.0	35.5	35.1	34.2	34.3	33.8	33.9	34.2	31.5	108/74	88	+ 5	
235464	After	50	37.28	34.70	34.8	35.5	35.3	35.4	35.1	34.4	34.6	34.3	34.2	34.4	31.8	103/65	75	+ 6	
E. B.	Before	119	37.02	34.21	34.5	34.5	34.0	34.4	34.1	34.0	35.0	33.7	34.1	34.0	34.3	104/74	71	+ 2	
24	During	68	37.03	34.22	34.4	34.6	34.0	34.6	34.1	34.0	34.8	33.8	34.4	34.1	33.5	117/83	80	+ 5	
	After	76	37.13	34.43	34.4	34.9	34.5	34.7	34.2	34.3	35.0	33.9	34.6	34.1	34.0	107/73	71	+ 7	
G. V.	Before	163	36.26	34.12	34.4	34.8	34.4	34.4	34.3	34.2	34.3	33.2	34.1	33.5	33.7	99/65	52	- 6	
19	During	115	36.33	33.90	34.3	34.7	34.1	34.4	34.1	33.9	33.6	33.3	34.0	33.2	33.1	111/74	62	-11	
39354	After	105	36.36	33.88	34.2	34.9	34.2	34.2	34.4	33.8	33.8	33.1	33.9	33.1	32.9	103/69	57	-10	
Averages	Before	88	36.78	33.92	34.5	34.5	34.3	34.4	34.0	33.8	34.7	33.5	33.6	33.0	32.1	105/69	61	- 4	
	During	50	36.85	33.95	34.5	34.5	34.4	34.6	34.3	33.9	34.3	33.6	33.4	33.6	31.2	117/80	82	- 4	
	After	60	36.89	33.98	34.5	34.6	34.5	34.4	34.2	34.0	34.6	33.6	33.9	33.5	31.4	112/74	69	- 3	

Data from Evans and Stewart.[1]

perature with a fall in hand temperature. For the whole group there was, on the other hand, a rise in foot temperature and a rise in blood pressure and in pulse rate.

The decrease in peripheral blood flow with smoking is an expression of the arteriolar constriction which takes place. There is a decrease in skin temperature. As the body is unable to lose as much heat through the skin in which there is arteriolar constriction the rectal temperature rises. Another instance in which this occurs in the human body was shown clinically by Evans and Stewart[6] in a patient who suffered from an adrenal pheochromocytoma. In this patient the peripheral blood flow was decreased, the rectal temperature was elevated, the skin was cold, and the heart rate was increased before operation when the patient exhibited an elevated blood pressure, even though there was marked elevation of basal metabolic rate. After removal of the tumor, the basal metabolic rate fell to normal, the peripheral blood flow increased, the rectal temperature fell, and the skin temperature rose.

When the changes resulting from smoking in these older persons are compared with the averages of six young individuals, the fall in peripheral blood flow, as we have already indicated, was slightly less (and in foot and hand temperatures was very much less) and the rise in blood pressure and pulse rate was less in the old age group. The effects of smoking standard cigarettes, therefore, in the older age group are essentially the same as in the younger normal age group, but they are quantitatively less.

The difference in magnitude of response to smoking in these older subjects may be due to the arterial system, in them being more rigid and less resilient than in the younger individuals. Alteration in response to stimuli with aging of the human organism is a common experience. For instance, it is well known that atropine increases the heart rate much less in an older individual than in a younger one. These changes, so far as the effects of smoking standard cigarettes are concerned, are the same as those found by Evans and Stewart[1] and Roth, McDonald, and Sheard[3] in young normal subjects.

It has been shown in these observations that the smoking of two cigarettes not only brings about alterations in the peripheral blood flow, blood pressure, and heart rate, skin temperature, and rectal temperature, while the cigarettes are being smoked, but the effects may still be present as long as *thirty minutes* afterward. It is apparent that with repeated smoking at short intervals these effects of smoking may be more or less continuous and persistent throughout the smoking period of the twenty-four hours.

Clinically, there did not appear to be any characteristics to differentiate the four patients in whom smoking increased the peripheral blood flow. In them, moreover, there was no significant change in blood pressure or heart rate on smoking, further indicating a basic difference in response.

Since smoking cigarettes is now shown in the older age group as well as in young subjects to give rise to arteriolar constriction and certain other effects on the cardiovascular system, the data now being reported indicate that smoking may be harmful in certain peripheral vascular diseases in which the blood supply to the periphery is already decreased. Since smoking decreases the peripheral blood flow and decreases the skin temperature of the hands and feet it is not out of order to ask whether or not it is wise to allow wounded and "shocked" soldiers and sailors to smoke in spite of the "lift" which they derive from smoking.

SUMMARY

The effect of smoking standard cigarettes on the peripheral blood flow was studied by means of a method with which the average amount of blood allotted to the periphery can be measured in cubic centimeters per square meter of body surface per minute. The peripheral blood flow was measured in seventeen patients who exhibited evidences of hypertension and coronary arteriosclerosis and who were in the older age group ranging from 38 to 81 years of age. Effects on the basal metabolic rate, blood pressure, and pulse rate were also recorded. Studies were made before, during, and after the smoking of one brand of regular commercial cigarettes. All observations were made with patients in a basal metabolic state at a room temperature of 27° C. and 45 to 50 per cent humidity.

1. As a result of smoking, the peripheral blood flow decreased in thirteen subjects and increased in four subjects. In the four showing increases, the peripheral blood flow decreased for single observations either during or after smoking but not sufficiently to counterbalance the average trend of increase in peripheral blood flow for the whole period of the observations. After cessation of smoking the peripheral blood flow continued to decrease in some and began to return toward the control levels in others.

2. The blood pressure rose and the pulse rate increased in the group in which smoking decreased the peripheral blood flow, but it was essentially unchanged in the group in which smoking increased the peripheral blood flow.

3. The rectal temperature rose as a result of smoking.

4. The average skin temperature decreased as a result of smoking.

5. These changes resulting from smoking are similar to those occurring in normal subjects.

6. The changes in peripheral blood flow, blood pressure, heart rate, rectal temperature, and average skin temperature (especially the temperature of the hands and feet) were, however, less marked in these patients in the later decades of life than in normal young subjects.

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ELECTROCARDIOGRAPHIC CHANGES IN EARLY SYPHILIS PRIOR TO AND UPON COMPLETION OF INTENSIVE ARSENOTHERAPY

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IN SYPHILIS, the blood stream is invaded early in the infection, and it is generally admitted that, during this period, the treponemas lodge in the various viscera.[1] Yet many observers[2] deny the early invasion of the heart, except on rare occasions, and have held that cardiac syphilis is essentially a late manifestation, usually occurring fifteen to twenty-five years after the original infection. Wilson and his co-workers[3] were convinced that reliable clinical evidence of electrocardiographic involvement of the heart or aorta during the primary and secondary stage must be exceedingly rare. Turner and White's[1] observations showed nothing conclusive to indicate changes in the heart muscle in the primary and secondary stages.

Our hospital unit had been receiving many untreated cases of early syphilis. In view of the conflicting opinions in the literature and also the lack of previous demonstrations of significant alterations in the electrocardiogram in early syphilis, it was considered opportune to investigate this problem. A report of our findings appears to be of interest.

METHOD AND PROCEDURE

Routine electrocardiograms were taken in one hundred consecutive cases of primary and secondary syphilis that were admitted to this general hospital for the twenty-day course of intensive arsenotherapy recommended at the time in this theater. Briefly outlined, the treatment consisted of the intravenous injection of 1 mg. Mapharsen per kilogram of body weight per day, the total dose not exceeding 75 mg. daily. The electrocardiograms were taken prior to, and upon completion of, the arsenotherapy. The conventional limb leads were obtained with the patient in a semirecumbent position, to exclude alterations attributable to changes in position. The galvanometer was standardized to a sensitivity of 1 cm. deflection per 1 millivolt. The patients were normal American soldiers who were admitted for untreated primary and secondary syphilis. The patients all received a complete medical examination before the commencement of therapy. Laboratory studies, in addition to the electrocardiogram, included a complete blood count, a platelet count, measurement of bleeding and coagulation time, urinalysis, determination of the sugar and nonprotein nitrogen, of the blood icterus index, intravenous hippuric acid function test, and examination of the spinal fluid. In the case histories given below, only the abnormal findings will be noted.

RESULTS

Four patients (4 per cent) of our series on admission showed definite alterations from the normal electrocardiogram. Following the twenty-day course of intensive arsenotherapy as previously outlined, the electrocardiograms in these cases had all become normal.

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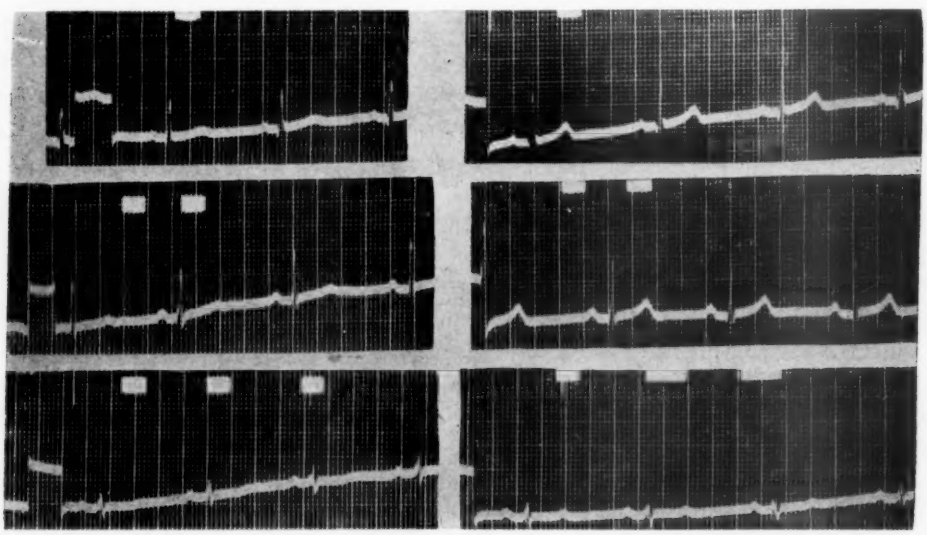
None of the patients with a negative quantitative Kahn test on admission showed any electrocardiographic changes, while four out of fifty patients (8 per cent) with primary and secondary syphilis and positive quantitative Kahn tests showed abnormal tracings. Two out of seven patients (29 per cent) with skin lesions of secondary syphilis and two out of ten patients (20 per cent) with a generalized lymphadenopathy had abnormal electrocardiographic findings.

The alterations were chiefly found in the final deflection. The T waves in four cases were abnormally low before treatment. In Lead I, the T waves were isoelectric in one case, almost isoelectric and slightly diphasic in another, and less than 0.5 mm. amplitude in every instance. In Lead II, the T waves were inverted in one case, isoelectric in another, and less than 0.5 mm. amplitude in every instance. In Lead III, the T waves were isoelectric or inverted in all the cases. Following the twenty-day course of arsenotherapy, the T waves increased in amplitude to normal levels in every instance (Figs. 1, 2, 3, and 4 inclusive).

There were at least six additional cases that showed definite increases in the amplitudes of the T waves following therapy; but, though the T waves were of low voltage prior to the therapy, the electrocardiograms were still within normal limits (Fig. 5).



A. *B.*

Fig. 1.—Case 1. *A*, Oct. 9, 1943, electrocardiogram prior to arsenotherapy showing abnormal T waves. *B*, Nov. 7, 1943, the T waves increased in amplitude following the twenty-day course of arsenotherapy.

Occasionally, there was low voltage of the initial complexes with some slurring, and the S-T segments were slightly depressed. In one instance, persistent ectopic ventricular extrasystoles were present; they disappeared only during the therapy. One case showed a shifting pacemaker which disappeared at the time of completed arsenotherapy.

In none of the cases was there evidence of any recent illness other than syphilis; nor was there any history of cardiovascular or allied diseases.

CASE REPORT

CASE 1.—A 29-year-old white man was admitted to the hospital with a history of a penile lesion of three weeks' duration and a generalized skin eruption of two days' duration. His health had always been excellent.

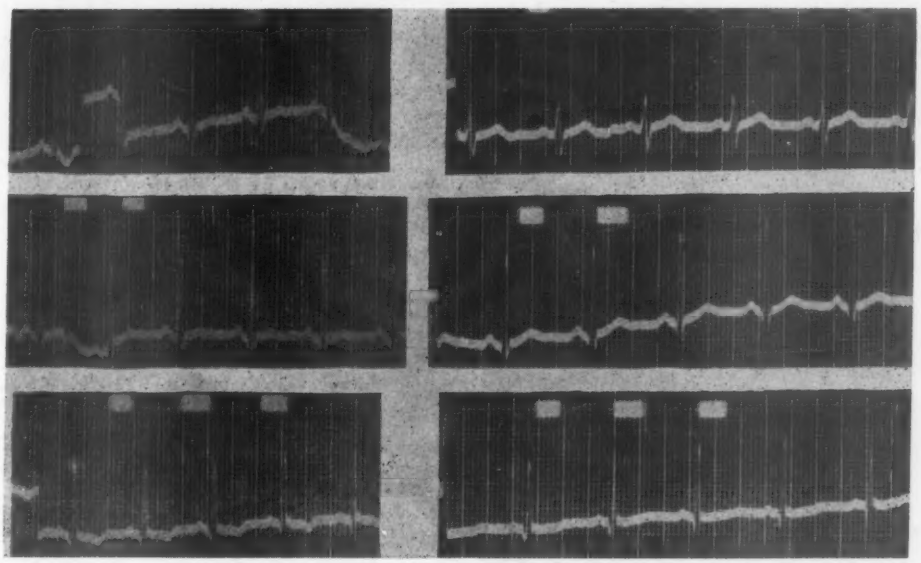
Physical examination revealed a well-developed young adult with a generalized maculosquamous skin eruption and a generalized shotty lymphadenopathy. There was a shallow ulcer on the shaft of the penis. The heart was of normal size and configuration; the heart sounds were of normal quality and the blood pressure was 128/78.

The quantitative blood Kahn test was positive in a titer of 160 units. An electrocardiogram taken prior to therapy showed a regular sinus rhythm of 66 per minute. The T waves were less than 0.5 mm. in amplitude in Leads I and II and slightly inverted in Lead III (Fig. 1, *A*). The second electrocardiogram, taken seven days after arsenotherapy, was completely normal (Fig. 1, *B*).

CASE 2.—A 23-year-old Negro was admitted to the hospital with a history of multiple penile lesions and a generalized skin rash of three weeks' duration. His health prior to this had always been excellent.

Physical examination revealed a thin, somewhat "anxious" young Negro. There were generalized discrete keratotic skin lesions, about 0.5 cm. in diameter, which were receding; lesions on the tongue, palate, and tonsils; condylomas on the scrotum; and shallow ulcers on the shaft of the penis. There was a generalized lymphadenopathy. The heart was of normal size and configuration and hyperactive to palpation. On auscultation, a transient soft systolic murmur was heard at the basal area with an accentuation of the second pulmonic sound. The blood pressure was 154 to 134/86.

The quantitative blood Kahn test was positive in a titer of 80 units. The first electrocardiogram taken prior to arsenotherapy showed a sinus tachycardia of 104 per minute. The T waves were almost flattened and slightly diphasic in Lead I, less than 0.5 mm. in amplitude in Lead II, and inverted in Lead III (Fig. 2, *A*). Ten days following therapy, the electrocardiogram had become normal with T waves of normal amplitude (Fig. 2, *B*).



A. *B.*

Fig. 2.—Case 2. *A*, Oct. 4, 1943, electrocardiogram prior to arsenotherapy showing abnormal T waves. *B*, Nov. 7, 1943, the T waves increased in amplitude following the twenty-day course of arsenotherapy.

CASE 3.—A 33-year-old Negro was admitted to the hospital with a history of a penile lesion of three weeks' duration. The past history was entirely negative.

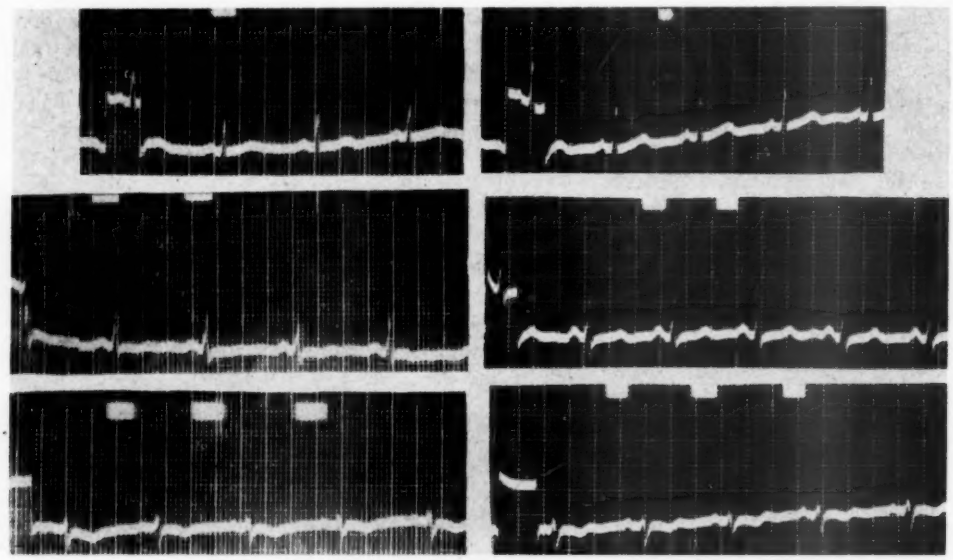
Physical examination revealed a well-developed young adult resting comfortably. His heart was of normal size and configuration; the sounds were of normal quality, and the blood pressure was 134/80. There were two small ulcers on the penis.

The quantitative blood Kahn test was positive in a titer of 10 units. The first electrocardiogram showed regular sinus rhythm of 84 per minute. The T waves were 0.5 mm. amplitude in Lead I, isoelectric in Lead II, and slightly inverted in Lead III (Fig. 3, *A*). Ten days after completion of arsenotherapy, the electrocardiogram showed an increase in amplitude of the T waves to a normal height (Fig. 3, *B*).

CASE 4.—A 23-year-old Negro was admitted to the hospital with a history of a penile lesion of three months' duration and a persistent headache with moderate weakness of several days duration. His past history was not significant.

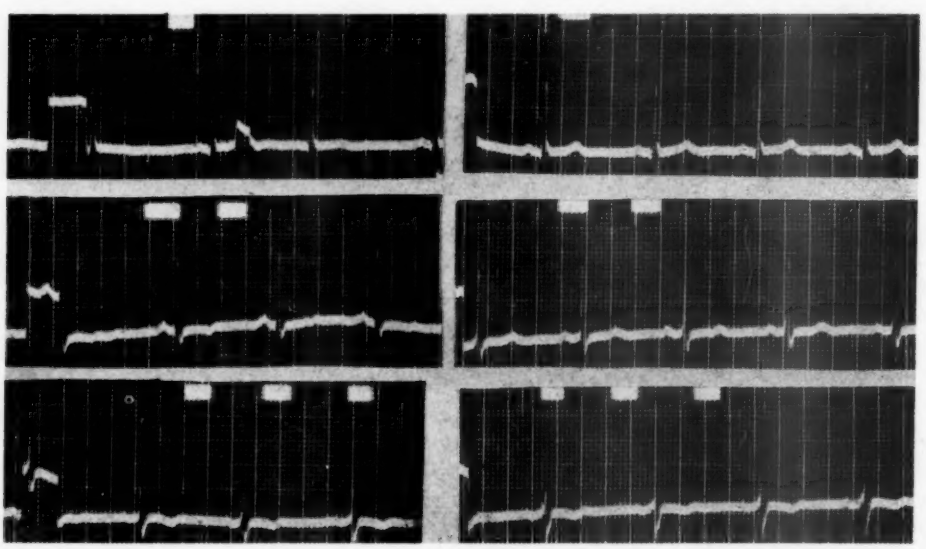
Physical examination revealed an adult Negro lying quietly, but uncomfortably, in bed. The heart was of normal size and configuration; the sounds were of normal quality, and the blood pressure was 120/86. Two shallow ulcers were present on the corona of the penis. A few discrete small nontender axillary and inguinal nodes were palpable. The deep reflexes were hyperactive but equal bilaterally. There was moderate nuchal resistance on flexion.

On admission, the quantitative blood Kahn test was positive in a titer of 80 units. The spinal fluid was clear with normal dynamics; there were 141 cells per cubic millimeter with



A. *B.*

Fig. 3.—Case 3. *A*, Oct. 4, 1943, electrocardiogram prior to arsenotherapy showing abnormal T waves. *B*, Nov. 4, 1943, the T waves increased in amplitude following the twenty-day course of arsenotherapy.



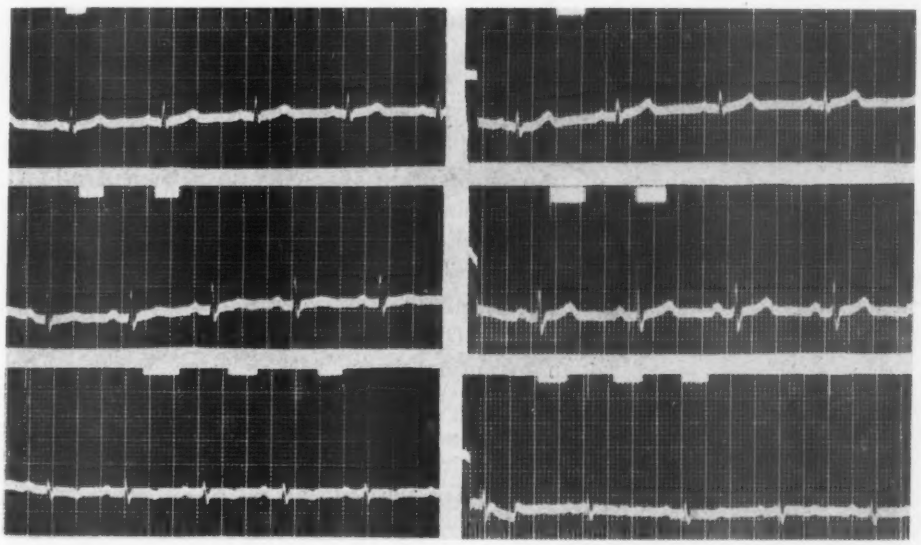
A. *B.*

Fig. 4.—Case 4. *A*, Sept. 9, 1943, electrocardiogram prior to arsenotherapy showing abnormal T waves. *B*, Oct. 9, 1943, the T waves increased in amplitude following the twenty-day course of arsenotherapy.

31 polymorphonuclears and 110 lymphocytes; total proteins, 56.2 mg. per cent; sugar, 62.3 mg. per cent; Kahn test, negative; and colloidal gold curve, 0012332000.

The electrocardiogram taken prior to massive arsenotherapy showed a regular sinus rhythm of 60 per minute. The T waves were isoelectric in Lead I and inverted in Leads II and III (Fig. 4, *A*). The second electrocardiogram taken seven days after completion of the arsenotherapy showed a return to normal with positive T waves of 1.4 mm. amplitude in Lead I and 1 mm. amplitude in Lead II (Fig. 4, *B*).

It was also noted in this patient that, during the therapy, the spinal fluid findings returned to normal; the quantitative Kahn test became negative; and the patient was entirely asymptomatic upon discharge.



A. *B.*

Fig. 5.—*A*, July 15, 1943, electrocardiogram prior to arsenotherapy showing low voltage T waves. *B*, Aug. 15, 1943, the T waves increased in amplitude following the twenty-day course of arsenotherapy.

DISCUSSION

There is a great divergence of opinion as to the frequency with which clinical, electrocardiographic, and radiologic evidence of involvement of the heart can be found in early syphilis. It seems to be the consensus among recent investigators that conventional forms of examination yield very little as ordinarily applied. Wilson and his co-workers (60 cases),[3] Turner and White (50 cases),[1] Arnett (25 cases),[4] and Ingraham and Maynard (27 cases),[5] all had found no significant alterations in the electrocardiograms of primary and secondary syphilis.

Yet earlier workers found clinical symptoms and signs of early invasion of the heart and aorta. Brooks (1921),[6] in a study of 300 cases of secondary syphilis, found clinical evidence of cardiac involvement in 8 per cent of the cases. Hermann[5] discussed a case of pericarditis in a patient with a severe roseolar rash of acute syphilis which cleared promptly with intensive arsenotherapy. Stokes[7] states, "There is every reason to believe, from what is known of the pathologic mechanism of the disease, that cardiovascular syphilis should be all but universal during the late primary and early eruptive stages of the infection." Warthin's work suggests that the myocardium is involved with great frequency as a blood stream infection, so that the invasion would be a priori in the secondary stage. It is established that spirochetes will invade the myocardium; this is evidenced by the ease with which they can be visualized in the myocardium in congenital syphilis.[8]

Coombs[9] describes an acute vascular inflammation in the early stage, even before the skin rash appears, which is called an acute coronaritis. Pathologically, there are small blood vessel changes, localized perivascular or more diffuse myocardial mononuclear cell infiltrations.

Master[10] observed six cases of syphilis with low voltage T waves. Unfortunately, there is no information given as to whether they were early or late cases of syphilis. One of the patients, aged 37 years, with syphilis of the larynx and bones and a 4-plus Wassermann test, received antisyphilitic therapy for one and one-half years. Following this, the Wassermann test was negative and a repeated electrocardiogram showed an increase in the amplitude of the T waves in Leads I and II. Master felt the flat T wave in these cases may have been due to a syphilitic involvement of the myocardium. One of us (Klotz) has observed a patient with syphilis of the bones whose electrocardiogram showed flat T waves. After six months of iodide therapy, there was marked clinical and radiological evidence of improvement in the bony involvement and the electrocardiogram showed an increase in the amplitude of the T waves.

In their observations of electrocardiographic changes in 23 cases of early syphilis following the five-day massive arsenotherapy (240 mg. Mapharsen daily) Geiger and his co-workers[11] were concerned mainly with the diminution, disappearance, or reversal of the original upright T-wave deflection during the therapy with subsequent return to normal levels within a few weeks. These changes occurred to a lesser degree with the twenty-day arsenotherapy regime in about 10 per cent of our series. However, it was noted that the T waves in many of their cases subsequently returned to levels higher than were present in the tracings taken prior to the onset of the therapy.

It is difficult to explain the absence of demonstrable electrocardiographic changes in the series of recent investigators. All our patients were soldiers on foreign duty who were received untreated, directly from their units. It was noted, in the series of Turner and White,[1] that all the patients had received at least three arsenic injections before the studies were made. Stokes,[7] in his discussion of the early detection of meningeal involvement, states, "It is important to realize that the age of the infection and the amount of treatment given the patient before the first spinal fluid examination will markedly influence the percentage of abnormality found." Perhaps this should also be applied to the detection of early electrocardiographic changes. In one of our cases (Case 4), the patient had evidence of early meningeal involvement in addition to the electrocardiographic changes; both became normal at the conclusion of the arsenotherapy.

It is probable that the T-wave changes observed in our cases are indicative of myocardial disturbances secondary to the syphilitic infection. That they reverted to normal so quickly with therapy is not unusual as similar observations have been made in other acute infections and deficiency states. In all our patients with early syphilis who have been treated with the twenty-day intensive arsenotherapy method the secondary lesions of the mucous membranes and skin usually healed within three to five days and always at the conclusion of the course of therapy. Since at this stage of the disease, the pathologic lesions are uniform in type, it is felt that the heart has healed in a similar manner.

SUMMARY

1. In a consecutive series of one hundred cases of primary and secondary syphilis, four cases were presented showing abnormal T waves in the electrocardiograms. These became completely normal following a twenty-day course

of arsenotherapy. Six additional cases showed low voltage T waves, which increased in amplitude at the completion of the arsenotherapy.

2. Other findings noted in isolated instances were low voltage with some slurring of the initial complexes, slight depression of the S-T segments, persistent ectopic ventricular extrasystoles, and a shifting pacemaker, all of which disappeared upon completion of the arsenotherapy.

3. It is felt that the electrocardiographic changes observed are indicative of myocardial disturbances in early syphilis which recovered following intensive arsenotherapy.

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STUDIES CONCERNING THE ETIOLOGY AND PATHOGENESIS OF NEUROCIRCULATORY ASTHENIA

IV. THE RESPIRATORY MANIFESTATIONS OF NEUROCIRCULATORY ASTHENIA

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ALTHOUGH the patient suffering from neurocirculatory asthenia (NCA) experiences various symptoms, those which appear to arise from dysfunction of the respiratory system incapacitate him most severely. The patient with NCA can endure excessive perspiration, hyperthermia,[1] occasional or frequent episodes of giddiness,[2] tremor, the sharp transient type of precordial pain,[3] and nervousness, but he seemingly is overwhelmed whenever tachypnea and dyspnea are part of the syndrome. And, unfortunately, easily induced tachypnea and dyspnea occur in over 90 per cent of patients with NCA.[7, 12] Furthermore, it has been found[3] that the tachypnea occurring in the patient with NCA is responsible in many instances for the tachycardia which also may arise in conjunction with the former manifestation of the syndrome. Wood[12] has pre-

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sented evidence, too, that suggests that the dull, persistent type of precordial pain frequently experienced by these patients is due to respiratory malfunction.

The exact causes for the respiratory distress of these patients are still unknown. Several investigators[6, 10] have suggested that the entire syndrome of neurocirculatory asthenia with all of its manifestations, might be one of hyperventilation, but this suggestion has been discarded by more recent investigators.[5, 11, 12] It was also suggested that the respiratory symptoms were due to cardiac dysfunction, but, in a previous study,[3] we were unable to detect any basic cardiovascular abnormality in patients with this syndrome.

Because of the importance of the respiratory system in neurocirculatory asthenia, studies were made of fifty-four of the sixty patients with NCA of our series, who complained of dyspnea. In these studies, an effort was made to determine (1) the nature and cause of the tachypnea and dyspnea and (2) the pathogenesis of the dull, prolonged type of precordial pain so frequently complained of. The results of these studies follow.

THE NATURE AND CAUSE OF THE TACHYPNEA AND DYSPNEA

A. The Organic Status of the Lungs.—Clinical surveys, teleroentgenograms, sedimentation rates, and multiple examinations of sputa for the tubercle bacillus were performed on each of the fifty-four patients with NCA studied. No evidence of active or chronic disease was found by these diagnostic measures in a single one.

Measurements of the vital capacity were obtained from fifteen patients who complained of experiencing severe dyspnea on slight exertion. It was found that their average vital capacity was 4,400 c.c., or 2.3 liters per square meter, which, according to the standards of Gross,[4] represented a value within normal limits. Thus it would appear certain that not only were the lungs of the patient with NCA free of disease, but they were also normal in ability to take in and expel sufficient quantities of air.

B. The Capacity for Holding the Breath.—In both organic pulmonary and cardiac disease of a degree severe enough to produce dyspnea, the breathholding time is also reduced and both processes seem to be dependent on the same etiological factors. Likewise in the patient with NCA subject to dyspnea, it has been observed[6, 12] that the breathholding time is reduced. In our series of patients with NCA, complaining of dyspnea on slight exertion, the average breathholding time was found to be 40 seconds (range: 25 to 60 seconds) which, when compared to the average breathholding time of 58 seconds (Range: 35 to 100 seconds), found in thirty normal individuals, represented a moderate but definite decrease. Furthermore, the breathholding time was found to be directly related to the severity of the dyspnea suffered, because in eleven patients subject to severe breathlessness on the slightest exertion, the average breathholding time was found to be even further reduced (average: 32 seconds). It seemed most likely, then, that the same mechanism underlying the dyspnea in the patient with NCA was also responsible for the diminution in duration of breathholding. Accordingly, the factors underlying the decrease in time of breathholding were investigated.

C. The Relation of Oxygen Excess to the Breathholding Capacity.—Five patients with NCA, complaining of severe dyspnea on slight exertion, and five normal persons were allowed to breathe pure oxygen for three minutes. At the end of this time, they were instructed to hold their breath as long as possible. It was found that the average breathholding time of the five patients

with NCA was 32 seconds before, and 34 seconds after, the respiration of oxygen. However, the breathholding time of the five normal subjects was 60 seconds before, and 90 seconds after, the same procedure. Thus, the normal person gained approximately 50 per cent in breathholding time, whereas no appreciable gain occurred in the patient with NCA. This suggested that the decrease in breathholding time (and, by inference, the dyspnea also) of the patients with NCA was not due to oxygen lack because they were not benefited by an excess of it.

D. The Relation of Oxygen Lack to Tachypnea and Dyspnea.—The same five patients with NCA and the five normal persons previously described, were then given pure nitrogen to breathe by mask, after basal respiratory and pulse rates had been obtained. They were instructed to signal with the right hand when they first experienced unendurable dyspnea. As Table I indicates, the patients with NCA, despite the fact that they were breathing no oxygen, exhibited no greater increase in respiratory or pulse rate than did the normal individual. Of even greater importance, they did not experience more rapidly occurring dyspnea than did the normal individuals, although they were deeply cyanotic fully thirty seconds before they signalled the onset of unbearable dyspnea. These observations indicated conclusively that neither the tachypnea nor the dyspnea of the patient with NCA was dependent on an oxygen deficiency, either in the blood or in the tissues, because it was obvious that as long as these patients were allowed to go through the sheer, but oxygen-profitless, mechanics of breathing, neither objective nor subjective differences in cardiorespiratory dynamics were observed between them and the normal subjects.

TABLE I. THE TIME OF ONSET OF DYSPNEA IN PATIENTS WITH NCA AND IN THE NORMAL PERSONS DURING THE INHALATION OF PURE NITROGEN

		BEFORE NITROGEN INHALATION		DURING NITROGEN INHALATION		
CASE	BREATH-HOLDING, MAXIMUM (SEC.)	RESPIRATORY RATE (PER MIN.)	PULSE RATE (PER MIN.)	TIME OF ONSET OF UNENDURABLE DYSPNEA (SEC.)	RESPIRATORY RATE (PER MIN.) AT END	PULSE RATE (PER MIN.) AT END
			Patients With NCA			
28	25	20	82	210	26	122
42	32	18	80	195	28	120
45	30	20	84	220	28	124
46	28	18	84	165	32	130
50	45	20	78	240	30	126
Average	32	19	82	206	29	124
			Normal Persons			
C-1	55	18	76	180	30	130
C-2	60	18	84	200	28	122
C-3	75	20	86	220	28	134
C-4	50	18	74	210	32	122
C-5	55	18	82	218	26	118
Average	59	18	80	205	29	125

E. The Relation of Carbon Dioxide Excess to Breathholding Capacity.—Although it was found that the diminution in breathholding and the occurrence of dyspnea in the patient with NCA were probably not due to a deficiency in oxygen supply, the possibility remained that these abnormalities in respiration were due to an abnormal increase in the blood gas, carbon dioxide. Accordingly, five patients with NCA and three normal persons were instructed to hyperventilate for seventy-five seconds (rate of respiration: 50 per minute) after

TABLE II. THE EFFECT OF HYPERVENTILATION ON THE BREATHHOLDING ABILITY OF PATIENTS WITH NCA AND OF NORMAL PERSONS

CASE	BEFORE HYPERVENTILATION		IMMEDIATELY AFTER HYPERVENTILATION	
	BREATHHOLDING MAXIMUM (SEC.)	CO_2 COMBINING POWER-PLASMA (VOL.%)	BREATHHOLDING MAXIMUM (SEC.)	CO_2 COMBINING POWER-PLASMA (VOL. %)
		Patients With NCA		
30	40	55	15	46
42	35	62	15	56
47	40	56	26	50
55	35	50	28	45
Average	38	56	21	49
		Normal Persons		
C-2	60	56	88	46
C-3	75	54	86	48
C-4	50	54	80	48
Average	62	55	85	47

control determinations had been taken of their breathholding capacity and the carbon dioxide combining power of venous blood. Immediately after the cessation of hyperventilation, a second determination of breathholding and of the carbon dioxide combining power of the venous blood was obtained. As Table II shows, although in both the normal person and in the patient with NCA, the blood carbon dioxide concentration was approximately equal and fell after hyperventilation by equal amounts, the breathholding ability of the patient was not only abnormally curtailed before hyperventilation, but failed to improve even after hyperventilation. These observations thus indicated that the decrease in breathholding time and, presumably also the dyspnea of the patient with NCA, were phenomena which were not due to an excess of carbon dioxide in the blood.

F. The Respiration During Effort.—Although it had been noted many times in the past that the respiratory and pulse rate of the patient with NCA might increase inordinately during effort, the observations strongly suggested that the tachypnea and dyspnea during effort were not due either to abnormalities in concentration of oxygen or to carbon dioxide in the blood. Since it was also found previously[3] that the cardiac abnormalities occurring in the patient with NCA during effort were conceivably initiated by the respiratory dysfunction, it seemed quite likely that the respiratory dysfunction was neurogenic or psychogenic in origin.

In order to study this possibility, a group of six patients with NCA, complaining of severe dyspnea on slight exertion, and six normal young adults were allowed to perform a test previously described[3] without preliminary introduction or orientation. It was observed (Table III) that the respiratory and pulse rates of the patients with NCA increased markedly and abnormally in comparison with those of normal persons. For example, the average respiratory and pulse rates in the patients with NCA, after only thirty seconds of performing the test, was 27 and 118 per minute, respectively, whereas it was 20 and 89 per minute, respectively, in the normal young adults. However, when the same groups performed the test after two practice trials (during which the test was discontinued approximately ten seconds after it was begun), it was observed (Table III) that the respiratory and pulse rates of the patients with NCA did not increase any more than did those of the normal persons taking the test. This improvement in the cardiorespiratory dynamics of the patient with NCA could not have been due to increased muscular efficiency in performing the test because

TABLE III. THE RESPIRATORY AND PULSE RATES OF PATIENTS WITH NCA AND NORMAL PERSONS DURING A SPECIAL EXERCISE TEST (BEFORE AND AFTER ORIENTATION)

CASE	BEFORE EXERCISE		DURING EXERCISE					
			AFTER 30 SECONDS OF EXERCISE		AFTER 60 SECONDS OF EXERCISE		AFTER 120 SECONDS OF EXERCISE	
	RESPIRATORY RATE (PER MIN.)	PULSE RATE (PER MIN.)	RESPIRATORY RATE (PER MIN.)	PULSE RATE (PER MIN.)	RESPIRATORY RATE (PER MIN.)	PULSE RATE (PER MIN.)	RESPIRATORY RATE (PER MIN.)	PULSE RATE (PER MIN.)
Before Orientation								
A. Patients With NCA								
21	20	80	24	100	28	110	30	120
23	18	88	24	120	30	124	32	122
24	22	92	28	124	32	122	34	128
25	20	82	32	128	34	130	32	136
26	22	88	28	116	26	124	28	130
27	18	82	24	120	28	128	30	134
Average	20	85	27	118	30	123	31	128
B. Normal Persons								
C-1	18	78	20	96	22	96	24	90
C-2	21	78	20	94	24	104	24	104
C-3	19	80	22	90	22	98	24	102
C-4	16	72	18	76	20	84	20	84
C-5	22	78	20	80	24	86	22	90
C-6	21	84	22	96	22	96	24	96
Average	20	78	20	89	22	94	23	94
After Orientation								
A. Patients With NCA								
21	20	76	20	86	24	98	26	96
23	18	82	18	94	20	100	24	100
24	18	80	20	90	20	98	22	100
25	20	72	22	86	24	98	26	98
26	20	86	18	88	20	94	22	98
27	18	80	20	88	22	96	22	96
Average	19	79	20	89	22	97	24	98
B. Normal Persons								
C-1	20	82	20	88	24	98	22	98
C-2	18	70	20	84	22	88	24	96
C-3	18	64	22	78	20	88	22	92
C-4	20	78	20	78	22	84	24	98
C-5	18	88	20	90	24	98	24	108
C-6	18	92	18	88	22	94	26	98
Average	19	79	20	84	22	91	24	98

their preliminary, orienting trials were too brief to allow such enhancement. Also, if sheer practice were the reason for their improvement, one would expect the normal adults to have shown a comparable improvement also, but, as Table III shows, they performed the test as well the first time as they did after the preliminary trials. It appears quite likely from these experiments that when some psychogenic or neurogenic element was eliminated by preliminary orientation, the previously observed, early, abrupt tachypnea and its accelerating effect on the pulse rate[3] was eliminated in the patient with NCA taking the test.

G. The Respiration at Rest.—Although the basic respiratory rate of the fifty-four patients with NCA at rest in bed was found to be exactly similar to that of normal persons; fourteen of the patients with NCA (26 per cent) were subject to dramatically sudden, inexplicable attacks of tachypnea and dyspnea which were associated with manifestations of a generalized sympathetic discharge and the *facial representation, but not the conscious realization, of anxiety.* When these episodes of spontaneous respiratory dysfunction were considered

with the previously described evidence that the respiratory dysfunction was not dependent on basic abnormalities in the lung, the heart, or on the concentration or exchange of blood gases, it became obvious to us that the fundamental disturbance underlying the respiratory difficulties of the patient with NCA, both at rest and during effort, was either a psychogenic or neurogenic one.

THE PATHOGENESIS OF THE DULL TYPE OF PRECORDIAL PAIN

A. Clinical Characteristics of the Dull Type of Precordial Pain.—In a previous article,[3] two types of precordial pain were distinguished as occurring either separately or together in the patient with NCA. In the same study, it was observed that one of these types, the sharp, transient pain, was found to be associated and apparently arising from actual, but temporary, cardiac dysfunction. The etiology, however, of the second type of pain (the dull, prolonged pain of the left chest with maximal intensity around the left nipple) was found to be, as Wood[12] suggested, of respiratory origin. Twenty-seven patients of our series (45 per cent) gave a history of experiencing this latter type of pain. Twelve of these patients also experienced the sharp, transient type, at times, but they were able to differentiate the two forms quite readily.

The onset of dull precordial pain was almost always preceded, either immediately or considerably earlier, by indulgence in vigorous exertion during which excessive tachypnea and tachycardia had occurred. The sensation of pain was described as "aching" or "sore" but never as sharp or lancinating in character. Its duration varied from ten minutes to many hours. Only five of the twenty-seven patients exhibited tenderness over the precordial area. It was observed further that, when suffering from this pain, the patient with NCA, without exception, avoided lying on the left side, for this position accentuated the intensity and duration of the symptom. Characteristically the pain was not aggravated by a *single* deep inspiration.

B. The Type of Respiration Exhibited With Dull Precordial Pain.—As Wood[12] pointed out, we also have observed that patients with NCA, subject to attacks of dull precordial pain, almost invariably used only the upper third of the chest in breathing. When the twenty-seven patients experiencing episodes of dull precordial pain were compared with twenty-three patients with NCA who did not experience this pain, and with ten normal individuals, it was found (Table VI) that, whereas twenty-four of the twenty-seven patients subject to attacks of pain, breathed exclusively, at rest, with the upper third of the chest, only four of the twenty-three patients not subject to attacks of pain breathed in this fashion. None of the normal subjects were observed to breathe in this fashion.

Similarly, it was found (Table IV) that the average maximal expansion of the upper third of the chest of the patient with NCA, having attacks of pain, was greater than the maximal expansion of the lower third (6.1 cm. compared with 5.8 cm.). This finding was in sharp contrast with the measurements of the chest expansion in the patient with NCA not subject to pain and with those of the normal individual. In the patient without pain, maximal expansion was in the lower third of the chest whereas in the normal individual, the average maximal expansion of the lower third of the chest was 3.4 cm. greater than that observed in the upper third (Table IV).

These observations made it clear that the patient who experienced attacks of dull, precordial pain, breathed in a different fashion than both the patient without pain and the normal person. Furthermore, the marked change in the

TABLE IV. THE RESPIRATORY CHARACTERISTICS OF PATIENTS WITH NCA, SUBJECT TO DULL PRECORDIAL PAIN, OF PATIENTS WITH NCA, NOT SUBJECT TO DULL PRECORDIAL PAIN, AND OF NORMAL PERSONS

CASE	TYPE OF RESPIRATION	UPPER CHEST EXPANSION, MAXIMUM (CM.)	LOWER CHEST EXPANSION, MAXIMUM (CM.)	EXPIRATORY PRESSURE, MAXIMUM (MM. HG)
	A. Patients With NCA Subject to Dull Precordial Pain			
1	Thoracic	-	-	46
2	Thoracic	6	7	75
3	Thoracic	-	-	55
5	Thoracic	5	6	—
7	Thoracic	8	8	—
9	Thoracic	5	5	74
16	Thoracic	7.5	9	64
20	Thoracic	4	2.5	46
21	Abdominothoracic	8.5	8	38
23	Thoracic	-	-	46
24	Thoracic	6	8	38
25	Thoracic	10	9	65
26	Thoracic	5	3	45
28	Thoracic	4	4.5	46
29	Thoracic	7	8.5	44
32	Thoracic	5	7	74
36	Abdominothoracic	4	2.5	84
37	Thoracic	-	-	66
39	Thoracic	8	6	60
40	Thoracic	4	4	70
41	Thoracic	6	5	52
42	Thoracic	7	9	46
44	Abdominothoracic	3.5	2	70
45	Thoracic	9	5	74
49	Thoracic	7	4.5	68
56	Thoracic	3	3	32
62	Thoracic	7	6	42
Average		6.1	5.8	57
	B. Patients With NCA Not Subject to Dull Precordial Pain			
8	Abdominal	7	9	70
11	Abdominal	-	-	90
13	Abdominal	4	5	110
14	Abdominal	4.5	5	98
17	Abdominal	6.5	8	68
18	Thoracic	4	4	78
19	Abdominal	7	9	120
22	Abdominal	4	6	90
27	Abdominal	5	4	88
30	Abdominothoracic	6	11	65
31	Thoracic	-	-	100
33	Abdominal	-	-	70
34	Abdominothoracic	4	6	100
35	Abdominothoracic	-	-	75
38	Thoracic	8	6	45
43	Abdominothoracic	9	14	—
47	Abdominal	9	12	80
48	Thoracic	7	9	65
51	Abdominal	4.5	9	88
60	Abdominal	-	-	96
61	Abdominal	6.5	8.5	110
63	Abdominal	9	9.5	84
64	Abdominal	5.5	8.5	94
Average		6.1	7.9	86
	C. Normal Persons			
C-1	Abdominal	6	10	100
C-2	Abodminal	6	9	116
C-3	Abdominal	9	10	120
C-4	Abdominal	2	6	100
C-5	Abdominal	4	9	—
C-6	Abdominal	4	5.5	140
C-7	Abdominal	5	11	118
C-8	Abdominal	9	11	122
C-9	Abdominal	3	7	—
C-10	Abdominal	6	9	126
Average		5.4	8.8	118

normal pattern of regional, maximal expansion of the chest in the patient subject to attacks of pain suggested that his peculiar type of upper chest respiration was probably of long standing. As a matter of fact, when these patients were asked to breathe in the lower chest or abdominal fashion, it was noticed that many of them were totally incapable of doing so, so fixed had their pattern of upper-chest breathing become.

Five patients with dull pain were observed fluoroscopically and the suspicion gained from clinical examination was confirmed: during quiet respiration, the diaphragm did not move significantly. This inadequacy of diaphragmatic movement was even more clearly suggested when the maximal expiratory pressure of the patient with attacks of pain was measured. It was found (Table IV) that the average maximal expiratory pressure of twenty-five patients with NCA, experiencing precordial pain, was 57 mm. Hg, whereas the average maximal pressure was 86 mm. Hg in twenty-two patients with NCA not subject to pain, and 118 mm. Hg in eight normal persons. It was possible, of course, that this striking decrease in the expiratory pressure of the patients subject to precordial pain was due to some generalized weakness of the total respiratory musculature, but this seemed unlikely in view of the fact that these patients were fully as robust as those not subject to pain. In view of the type of upper-chest respiration, and the observed inertia of the diaphragm, it seemed most likely that the impairment of expiratory pressure in the patient with NCA subject to pain was due to the lack of efficient or total diaphragmatic participation in the process of expiration.

C. The Production and Abolition of Dull Precordial Pain in Patients With NCA.—The preceding observations demonstrated that the patient with NCA, subject to attacks of precordial pain, breathed in a different manner than either the patient not subject to pain or the normal person. These studies did not prove, however, that the pain was caused by this difference in mode of respiration. Likewise, the abolition of dull precordial pain by anesthetization of the intercostal musculature in the precordial area, as reported by Wood[12] cannot be construed as unequivocal proof that this pain arose because of upper-chest breathing. Nevertheless, these observations were quite suggestive and if, in addition, it were found that the pain could be provoked or intensified in susceptible patients by experimental accentuation of upper-chest breathing, and diminished or abolished in these patients by experimental inhibition of upper-chest breathing, the evidence would be quite conclusive for the assumption that the dull type of precordial pain was caused by the method of respiration.

Accordingly, fifteen patients with NCA, subject to frequent attacks of dull precordial pain following very slight exertion, and five normal young adults were asked to breathe deeply and rapidly for two minutes at a rate of 40 respirations per minute. At the end of this time, they were asked only how they felt, while no specific reference was made to the possible presence of precordial pain. Each of the patients complained of dizziness, and nine complained of dull precordial pain which they stated was identical with that which they previously had experienced following exercise. The normal persons had no symptoms other than slight lightheadedness.

In another experiment, eight patients with NCA, subject to frequent and seemingly spontaneous attacks of dull precordial pain lasting from twenty minutes to several hours during each day, were instructed to expire all possible air from the lungs. Adhesive tape was then applied to the entire chest, down to the level of the eighth rib, in such a manner that upper-chest breathing was markedly

reduced; this forced them to resort to lower-chest and abdominal breathing. This adhesive-tape restraint was left on the patients for six days, and, during the last four days of this period, none of the patients experienced any attacks of pain. When the adhesive tape was removed, however, it was observed that all of the patients reverted immediately to their previous method of upper chest respiration, and within a period of twenty-four hours, all of them again began to experience attacks of dull, precordial pain.

D. The Production of Dull Precordial Pain in Normal Young Adults.—Fifteen normal young adults who never had experienced precordial pain were selected for this experiment. They were directed to indulge in strenuous exertion of a standard type for three days (trotting 600 yards on three separate occasions during an afternoon). After this control period, the chests of five of these subjects were splinted with adhesive tape as described previously. In the remaining ten subjects, however, the chest was bound with adhesive tape in such a manner that the lower third of the chest and the upper half of the abdomen were immobilized, so that they were forced to breathe almost exclusively with the upper half of the chest. The fifteen subjects were then instructed to engage again in the same exercise (daily) which they previously had taken. Although none of them had noticed any symptoms during the control period, it was noted that considerable tachypnea and dyspnea occurred in the ten subjects forced to breathe predominantly with their upper chest, whenever they indulged in the standard exercise. Eight of the ten subjects whose lower chest was immobilized, began to complain, on the second day of the experiment, of dull, aching precordial pain which came on about an hour after the performance of the last exercise of the afternoon. On the third day of the experiment, nine of the ten subjects, who were forced to breathe with the upper chest, complained of precordial pain. The adhesive tape restraints were removed from all on the fourth day, but the exercises were continued. Following the removal of the adhesive tape, the subjects previously experiencing precordial pain after exercise, became symptomless. At no time during the experiment, did any of the five adults whose upper chest was splinted, complain of precordial pain.

DISCUSSION AND SUMMARY

Evidence was obtained in the preceding studies that the tachypnea, dyspnea, and diminution in breathholding, so frequently found in the patient with NCA, were respiratory dysfunctions which were not caused by either disease or organic abnormality of the lung. It was also found that these functional respiratory abnormalities were not caused by any quantitative peculiarity of the blood gases or by defective utilization of these same gases by the tissues. In a previous study[3] it was discovered that the respiratory disturbances did not arise from cardiac dysfunction but, as a matter of fact, the disturbances in respiration influenced the cardiodynamics. On the other hand, the normality of the respiratory processes in patients with NCA while performing an exercise test (which, prior to mental or emotional orientation, they performed only with considerable tachypnea and dyspnea), strongly suggested that, when respiratory abnormalities did occur in these patients, they were not initiated by any organic or functional defect in the cardiorespiratory system. Finally, our observation of the spontaneous occurrence of sudden, inexplicable attacks of tachypnea and dyspnea accompanied by manifestations of sympathetic discharge in many patients with NCA, at rest in bed, indicated conclusively that the respiratory difficulties encountered in neurocirculatory asthenia are of psychogenic or neurogenic origin.

The dull type of precordial pain so frequently found in the syndrome of neurocirculatory asthenia was discovered to result from the method of respiration employed by the susceptible patient, a method in which the diaphragm was minimally, and the intercostal musculature maximally, utilized. The experimental production and abolition of precordial pain in both the susceptible patient with NCA and the normal person, by the employment of measures altering the manner of respiration, further indicated the pathogenesis of this manifestation of neurocirculatory asthenia. The localization of this pain in the precordial area of the chest was considered to result from the traumatic effect of the contracting heart on this portion of the intercostal musculature, as suggested by Wood.[12]

In previous articles,[1-3] evidence was presented which suggested that hypothalamic dysfunction was the mediating agent in the clinical emergence of somatic manifestations of neurocirculatory asthenia. In the present study, any correlation of the respiratory manifestations of the syndrome with hypothalamic dysfunction is difficult to prove. It is well known,[8, 9] however, that hypothalamic dysfunction may lead to respiratory abnormalities. It should be mentioned also that the spontaneous attacks of tachypnea and dyspnea associated with sympathetic manifestations of anxiety (without conscious experience of emotion on the part of the patient), which was observed by us in the patients with NCA at rest in bed, could be considered as strikingly similar to the behavior of the experimental animal whose hypothalamus had been stimulated, as described by Ranson.[8]

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CARDIAC ANEURYSM WITH SPONTANEOUS RUPTURE

Report of Two Cases

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A VENTRICULAR aneurysm of the heart, ominous in nature and seemingly a portent of danger because of its thin, scarred wall, seldom causes death by virtue of spontaneous rupture.[1-3] The usual terminal event is either slowly progressive cardiac failure or a cerebral embolus originating from a mural thrombus within the aneurysm.[1]

Cardiac ventricular aneurysms may develop from various diseases of the heart. The most common lesion, comprising 85 per cent of the cases, is myocardial infarction following atherosclerotic occlusion of a coronary artery. The small percentage that remains develops secondarily to syphilitic myocarditis, rheumatic necrosis of the myocardium, myocardial abscesses from infective endocarditis, congenital defects, and trauma.[2, 4, 5]

The development of a cardiac aneurysm following myocardial infarction is not a rare complication. A survey of 7,200 autopsies performed at the Pennsylvania Hospital reveals that death was caused by myocardial infarction, subsequent to atheromatous changes of the coronary arteries, in 141 cases. Such lesions as so-called "myocarditis" and rheumatic, syphilitic, and embolic changes are not included in this study. Cardiac ventricular aneurysm occurred in eleven of these 141 cases of myocardial infarction, giving an incidence of 8 per cent. Parkinson and his co-workers[2] concluded from the published postmortem statistics of six separate groups of observers that cardiac aneurysm occurred in 9 per cent of similar cases. In our series of 7,200 successive autopsies, cardiac aneurysm developed in 1.5 per 1,000 cases. Lucke and Rea,[6] in a comparable survey of 12,000 autopsies, found an incidence of 1.1 per 1,000.

Spontaneous rupture occurred in two of our eleven cases of cardiac aneurysm (18 per cent). Thurnam[7] (1836) and Hall[8] (1903) reported a spontaneous rupture incidence of 10 per cent and 15 per cent, respectively. In light of the relative infrequency of spontaneous rupture of cardiac ventricular aneurysm, it seems justifiable to report in detail the two following cases.

REPORT OF CASES*

Case 1 (History No. 68294).—*First Admission:* J. M., a 62-year-old Puerto Rican male "kitchen worker," entered the hospital on May 30, 1944, with a chief complaint of pain in the anterior part of the chest of thirty-six hours' duration. Except for recent tiredness, weakness, and intermittent pain in the anterior part of the chest, he had been in his usual good health. Thirty-six hours before admission, he experienced a sudden severe pain over the whole anterior part of the chest; the pain radiated to the left scapula, and was associated with a cold sweat. One episode of vomiting relieved the pain slightly; however, the precordial pain continued in moderate degree until the time of entry. His past history was not contributory. He had had no exertional dyspnea, orthopnea, ankle edema, or cough.

Physical examination revealed a well-developed and well-nourished elderly man in no acute distress. The temperature was 98° F.; the pulse rate, 100 per minute; and the

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respiratory rate, 24. The blood pressure was 140/80. The heart was markedly enlarged to the left, the rhythm was regular, the cardiac sounds were of poor quality, and no murmurs were heard. The lungs were clear to percussion and auscultation. The abdomen and extremities were not remarkable.

The leucocyte count was 16,800 per cubic millimeter; the erythrocyte count was 4,100,000; and the hemoglobin was 15 Gm. An x-ray film of the chest showed a markedly enlarged heart to the left and posteriorly. The lung fields were not remarkable. An electrocardiogram, taken on May 31, 1944, approximately twelve hours after admission, revealed a low amplitude of T_1 and widened ventricular complexes. A second tracing, taken on June 5, 1944, showed a shortening of the ventricular complexes and elevation of the S-T segment in Leads II, III, and IVF. These changes were interpreted as indicating "active myocardial pathology, most likely due to a recent myocardial infarct."

The patient was kept in bed for five weeks. His temperature was of the low-grade, intermittent type for the first two weeks, with gradual return to normal. He was discharged in an improved condition on July 6, 1944.

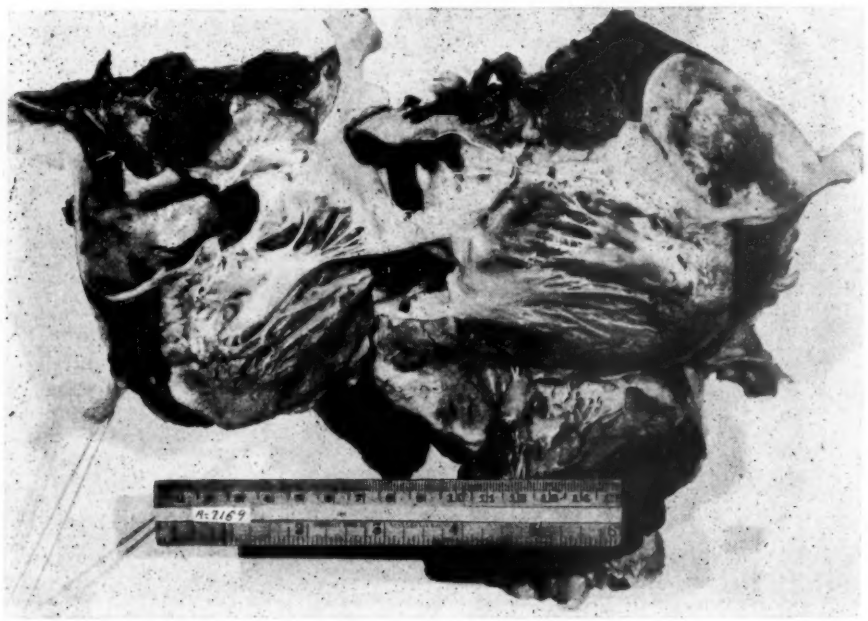

Fig. 1.—Sectioned aneurysm of the posterior wall of the left ventricle with rupture (arrow). Note the extensive hemopericardium.

Second Admission: He remained asymptomatic until the day of re-entry, Oct. 9, 1944, when a severe substernal pain awoke him, and he found himself drenched with cold perspiration. He vomited several times.

Physical examination revealed an acutely ill man with slight cyanosis. His temperature was subnormal; the pulse rate was 120 per minute but very weak, and the respiratory rate was 32. The blood pressure was 50, systolic; the diastolic was unobtainable. There was no venous congestion of the neck. The cardiac sounds were very feeble, no murmurs were heard, and there were no precordial pulsations. There were a few moist râles at the bases of the lungs.

An electrocardiogram taken a few hours after arrival revealed slight right axis deviation and diphasic T_2 and T_3 "suggestive of a developing posterior myocardial infarct."

During the patient's hospitalization, the blood pressure never rose above 66/54. About forty hours after entry, as he lay slightly dyspneic and cyanotic in an oxygen tent, he suddenly had a generalized convulsion; he screamed as if in agonizing pain and died immediately.

Post-Mortem Findings (A. 7169):* Thoracic cavity: The left pleural cavity was filled with 2,500 c.c. of blood which had compressed the left lung. The right pleural cavity contained 650 c.c. of cloudy straw-colored fluid. The heart was slightly displaced to the right.

*Unessential pathologic findings in this and the next case are omitted.

Heart (gross): The heart was greatly enlarged. The striking feature was the large aneurysmal sac projecting from the posterior wall of the left ventricle in the region of the septum (Fig. 1). This aneurysm measured approximately 10 cm. in diameter and had a 4 cm. orifice near the interventricular septum. It was filled with fresh blood as well as some organized clot at the periphery. The wall of the sac was extremely thin in places and was partially adherent to the pericardium. There was little or no muscular tissue in its wall. The aneurysm had ruptured into the pericardial space through a ragged tear about 1.5 cm. in diameter, and from there it broke into the left pleural cavity. Elsewhere the wall of the left ventricle was somewhat thickened, measuring 20 mm. in diameter. The left ventricle was a little compressed by the hemopericardium. The chamber of the right ventricle was greatly compressed by the encircling blood in the pericardial space. The valves were not particularly remarkable. The coronary vessels were slightly tortuous. There were a few areas of sclerosis, although no definite point of complete obstruction was found. Apparently the changes in the coronary vessels responsible for the aneurysm were in the circumflex branch.

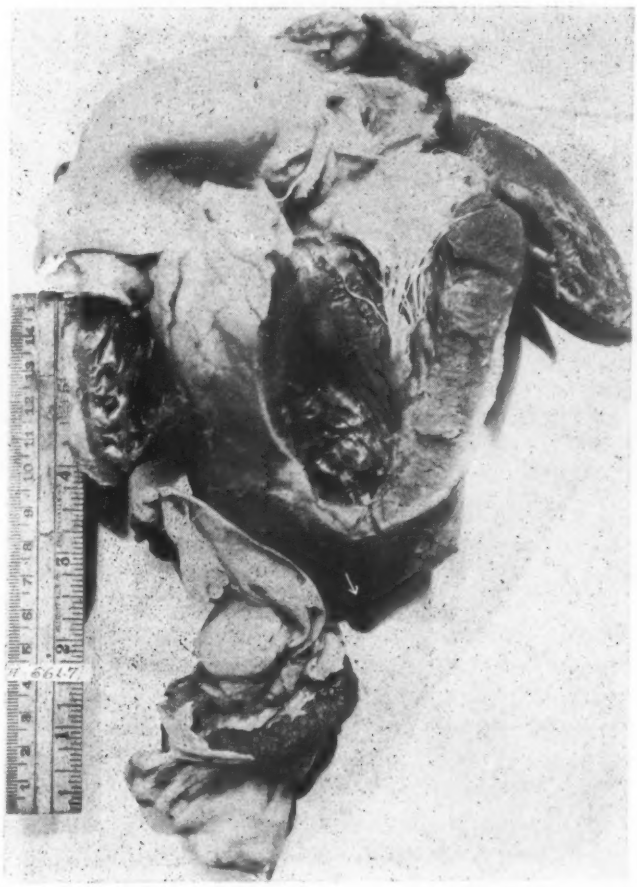

Fig. 2.—Aneurysm of the anterior wall of the left ventricle involving the apex with rupture (arrow).

Heart (microscopic): Sections through the aneurysmal wall revealed an extensive scarring of the myocardium with degeneration of many of the myocardial cells, as well as hypertrophy and hyalinization of the fibrous tissue. The myocardium from areas near the sac showed a slight degree of fatty infiltration and became more scarred as one approached the aneurysmal wall. In the sac wall proper, there was complete obliteration of the muscle fibers. The pericardium was adherent to the epicardium and blended with it over the aneurysm. However, the pericardium and epicardium were separated at the periphery of the aneurysm by an organizing blood clot. The wall of the aneurysm was composed of a dense hyalinized union of endocardium, scarred myocardium, epicardium, and pericardium. The coronary vessels showed atherosclerosis, and the arterioles were markedly narrowed.

CASE 2 (History No. 58149).—D. O'B., a 52-year-old male laborer, walked into the Accident Ward of the hospital on March 21, 1941, complaining of chest pain. A few minutes after arrival, before he could be examined, he suddenly died. He had been seen in 1939 for a "traumatized hand," and again in 1940 for a "dermatitis of the left arm." There were no cardiac complaints during these visits.

Post-Mortem Findings (A. 6617): Thoracic cavity: There were 700 c.c. of clear straw-colored fluid in the left pleural cavity, and 100 c.c. on the right. The heart was in its normal position.

Heart (gross): The pericardium was distended by 700 c.c. of blood. The apex of the heart was fastened to the pericardium by old, fibrous adhesions except at its very tip. After opening the pericardium, a large aneurysm of the anterior wall of the left ventricle involving the apex was revealed (Fig. 2). This aneurysmal sac did not communicate with the ventricular cavity by means of a narrow neck but rather with its entire diameter. The wall of the aneurysm was thin, being composed of epicardium, a slight amount of necrotic myocardium, and endocardium. The sac measured 6.5 cm. in diameter. The myocardium about the aneurysm was soft, gray, and necrotic. There was a tear 3 cm. long at the apex of the aneurysm. The right side of the heart was not abnormal. There were no valvular lesions. The ostia of the coronary arteries were normally wide. On gross section of the coronary arteries, there was moderate arteriosclerosis throughout their course, but there was little calcification of the intima. No absolute obstruction of the coronary lumina was found. However, about 2 cm. distal to the origin of the anterior descending branch, there was an area of very marked narrowing.

Heart (microscopic): In sections of the aneurysmal wall near the apex, there were large areas of comparatively fresh uniform necrosis of the myocardium. However, fibroblasts and capillaries were already beginning to organize this necrotic tissue. Granulation tissue that was replacing muscle fibers was also proliferating on the epicardial surface of other areas of the anterior wall of the left ventricle. A varying amount of subacute inflammatory exudate was present in the epicardium. In a section of myocardium from the base of the left ventricle, there was diffuse hypertrophy of the muscle fibers and perivascular scarring. The myocardium of the right ventricle was not remarkable. The lumen of the anterior descending branch of the left coronary artery near the apex was markedly distorted by large intimal fatty and calcified plaques, but no complete obstruction was seen. There was also an area of fresh coagulation necrosis in its intima.

DISCUSSION

The original account of cardiac ventricular aneurysm seems to have been made by Galeati[9] in 1757. Subsequent to this, numerous observers postulated various theories pertaining to the causes and development of this lesion. However, it was not until a century later that the present concept of pathogenesis was crystallized.[10] We now know that, following an occlusion of a coronary artery, the myocardium becomes necrotic. In time, the muscle fibers are replaced by connective tissue. If, during this process, the affected area is not strong enough to withstand the intraventricular pressure, then a gradual bulging of the ventricular wall takes place. The resulting aneurysm may be saccular, having a small orifice; more commonly, it may be a large bulge that is not sharply demarcated from the ventricular cavity. The aneurysmal wall is usually very thin, being composed mostly of dense, firm, fibrous tissue. It may or may not contain a few muscle fibers and deposits of calcium. A mural thrombus is often present.[1, 2, 5, 10, 11]

Of course, the relative age of the aneurysm when rupture occurs will determine the composition of the aneurysmal wall at the time of death. If the rupture is delayed, giving the aneurysm ample time to develop, then it will have a wall of well-organized connective tissue. Muscle fibers will be practically extinct. An example of this is seen in the first case. On the other hand, if the rupture occurs while the aneurysm is developing from an area of fresh myocardial infarction, then the wall of the aneurysm at time of death will be com-

posed largely of necrotic muscle cells with little fibrous tissue and organization. This is seen in the second case. The pathologic process in the two cases is the same. The only difference lies in the stage of development reached when rupture occurs.

The time that the infarcted myocardium gives way to aneurysmal dilatation has not been determined. It seems logical that aneurysmal development occurs during the period of myocardial necrosis and softening, which is most marked during the first two weeks after the coronary occlusion.[1] The fact that the degree of myocardial softening is a predisposing factor in spontaneous cardiac rupture following myocardial infarction substantiates this view.[12] It is further supported by the experiments of Sutton and Davis[13] who showed in dogs that aneurysmal development was less likely to take place if the rest period after myocardial infarction was extended during the phase of myocardial softening.

A cardiac ventricular aneurysm usually involves the anterior wall of the left ventricle, often including the apex, simply because the anterior descending branch of the left coronary artery is most commonly occluded. In spite of the fact that the posterior wall of the left ventricle is frequently infarcted, aneurysm here is relatively rare. An aneurysm of the right ventricle occurs least of all.[2, 4, 5, 10]

The clinician's interest in cardiac ventricular aneurysm is at present centered on ante-mortem diagnosis. Its symptomatology and physical signs have been extensively described.[1, 2, 4, 10, 14] The significant features in this regard are: (a) a history of a previous coronary occlusion; (b) failure to observe the approved period of rest in bed after a myocardial infarction; (c) a forceful and diffuse cardiac thrust, being most marked within or outside the midclavicular line, usually at the level of the fifth rib; and (d) a very weak and feeble first sound at the apex. The blood pressure, murmurs, and a gallop rhythm are unreliable guides. The physical signs are dependent upon the location of the aneurysm, and are most commonly found if the lesion is at the apex.

Radiological examination has become the most important aid in diagnosis. However, a cardiac aneurysm may be present and yet give no x-ray evidence.[11] To avoid oversight, roentgenograms should be made in the anteroposterior and oblique positions and checked by fluoroscopy.[15] If the lesion is at the apex, it may often escape detection because in this position the silhouette may appear merely as an elongation of the apical portion of the heart, or the lesion may be buried in the diaphragm.[2, 14] A sharply defined, localized bulge and a paradoxical pulsation, i.e., expansion of the sac during systole and a decrease in its size during diastole, are pathognomonic.[11, 16]

The role of the electrocardiogram as an aid in diagnosis of cardiac ventricular aneurysm has been claimed by Fulton[1] to be "of importance only as it may add to the evidence of myocardial infarction and assist in localizing the lesion in the anterior or posterior part of the ventricle." A similar opinion is also held by Parkinson and co-workers,[2] Dressler and Pfeiffer,[14] and Sigler and Schneider.[15] On the contrary, Eliaser and Konigsberg[17] confirmed Nordenfelt's[18] findings that the electrocardiogram may be of considerable diagnostic value. They believe that one of two types of electrocardiographic syndromes is present in 63.7 per cent of cases of aneurysm of the left ventricle following coronary occlusion. They feel that these syndromes are presumptive signs of the lesion, and when found should stimulate further diagnostic investigation. One type has "a downward directed major deflection in Lead I, with inversion of the

T wave and an upright P wave. The ventricular complex in Lead III is upright." The other type presents "ventricular complexes directed downward in Leads II and III with an upright major deflection in Lead I that may or may not be of low amplitude."

Cardiac ventricular aneurysm does not hold an immediate hopeless prognosis as is commonly thought. This lesion has quite a variable course, for the patient is always subject to repeated coronary occlusion, development of congestive failure, embolism, or rupture. Yet, ventricular aneurysm is not infrequently compatible with one or two years of moderately active life.[1, 2, 4]

SUMMARY

1. Cardiac ventricular aneurysm is not a rare complication of myocardial infarction. Yet, it seldom causes death by virtue of spontaneous rupture.

2. Atherosclerotic coronary occlusion is responsible for 85 per cent of the cases of cardiac aneurysm.

3. Two cases of cardiac ventricular aneurysm that terminated in rupture are herewith presented.

4. The etiology, incidence, pathogenesis, site, prerequisites for ante-mortem diagnosis, prognosis, and course of this lesion are briefly presented. The roles of x-ray and electrocardiography are discussed.

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THE RELATIVE INCIDENCE OF RHEUMATIC VALVE DISEASE IN NEW YORK AND COSTA RICA AND ITS BEARING ON THE RHEUMATIC ORIGIN OF CALCAREOUS AORTIC STENOSIS

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STENOSIS of the aortic valve occurring in conjunction with deformities of other valves is generally believed to be rheumatic in origin. When it occurs without associated lesions of other valves, the etiology is less apparent. The three major opinions that have been expressed about the origin of this second group are (1) that the lesion is invariably the end result of rheumatic endocarditis;[1-8] (2) that it is primarily noninflammatory and the end result of a degenerative process analogous to sclerotic processes that occur in other parts of the vascular system;[9-12] and (3) that the lesion is sometimes the result of rheumatic disease and sometimes the result of degeneration followed by calcification.[13-20]

The chief reasons for supporting the theory of the rheumatic origin of this form of valvular disease are as follows. A history of rheumatic fever earlier in life can be obtained in a significant number of cases (Christian[1] and Cabot[21]). Secondly, the lesion itself does not differ in appearance in any striking detail from that known to be the result of rheumatic infection, for example, in those cases in which the mitral valve is also deformed.[7, 8, 21] Finally, evidences of rheumatic inflammation are sometimes found in the diseased valve itself or in other parts of the heart on histologic study.[5-8]

There are, however, a number of formidable objections that have been raised to dispute the view that rheumatism is the invariable cause of aortic stenosis. Acute rheumatic endocarditis limited to the aortic valve is seen much less often than is stenosis of that valve alone for example.[22] Most series of cases reported show a striking preponderance of stenosis of the aortic valve in males,[11, 12, 17, 18, 21] whereas all the other known types of rheumatic lesions occur about equally in both sexes. Calcareous aortic stenosis is seen in a much older age group than are the proved forms of rheumatic disease.[21] Finally, mild degrees of calcification of the base of the aortic valve without deformity occur frequently in older age groups, particularly in males. Calcareous aortic stenosis has been interpreted as an extension of this process in certain susceptible individuals with advancing age. There are thus several reasons for accepting or denying each of the three opinions that have been expressed concerning the genesis of this lesion.

The incidence of rheumatic heart disease is believed to vary in different parts of the world and in different racial and economic groups. If this is so, it is possible to use this variation to obtain evidence as to whether or not calcareous aortic stenosis is always the result of rheumatic fever. In necropsy

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statistics that show a high incidence of rheumatic heart disease, the incidence of calcareous aortic stenosis should be correspondingly high. Conversely, if in a series of necropsies, the incidence of proved types of rheumatic heart disease is low, then calcareous aortic stenosis should also be infrequent. Deviations in the relative incidence of these lesions would suggest that rheumatic disease does not play an important role in the development of calcareous aortic stenosis.

The present report is an attempt to elicit information along these lines by comparing the incidence of rheumatic heart disease and calcareous aortic stenosis in three independent necropsy series using identical methods of analysis. The analysis was made on (1) 4,860 consecutive autopsies performed at Bellevue Hospital in New York City, (2) 5,700 consecutive autopsies performed at Long Island College Hospital and the Long Island College of Medicine division of Kings County Hospital in Brooklyn, New York, and, (3) 4,900 consecutive autopsies performed at the Hospital San Juan de Dios in San José, Costa Rica.

The sex and age distribution by decades was recorded for the entire group in each series. Each included a large, but variable, number of stillbirths and infantile deaths. There was a lesser number of childhood deaths. In the Long Island series 30.2 per cent of the autopsies were done on individuals less than 10 years of age, while in the Bellevue series only 10.1 per cent fell into this age period. Since rheumatic heart disease does not usually develop in infancy or early childhood, inclusion of this age group would make any comparison of rheumatic heart disease between the different hospital series inaccurate. The groups of persons who died before they reached the age of 10 years are, therefore, excluded from the tabulations. With these groups omitted, the Bellevue series is reduced to 4,370 of which 3,134 (71.7 per cent) were males, and 1,236 (28.3 per cent) were females. The Long Island series is reduced to 3,976 of which 2,361 (59.4 per cent) were males, and 1,615 (40.6 per cent) were females. Similarly, the Costa Rican series becomes 4,209 with 2,618 (59 per cent) males and 1,691 (41 per cent) females.

Cases included in the rheumatic group were those in which there was stenosis, insufficiency, or verrucous endocarditis of the mitral valve alone, or of both the mitral and aortic valves. In some of these the valves on the right side of the heart also had lesions. There were no examples, however, in any of the series of right-sided valve involvement without concomitant damage to the mitral and aortic valves. These cases are therefore not listed in separate categories. Cases of bacterial endocarditis were included only if pre-existing rheumatic damage to the mitral valve was demonstrable. The instances in which only the aortic valve was damaged are included in a separate category. Cases of syphilitic lesions of the aorta involving the aortic valves are excluded as are those cases in which the aortic valve was calcified at its attachment but in which the valves appeared to be competent. The results are recorded in Table I. It may be seen that among the cases of definite rheumatic lesions, i.e., those in which the mitral valve is damaged, there are certain features that are consistent for all three series and a few that are variable.

The consistent findings are the following. First, in each of the three series, mitral stenosis is more common in women than in men. Second, relatively the same proportion of mild and acute to stenotic lesions is seen in each of the three series. Third, when the incidence of each type of rheumatic valvular lesion is compared in each of the three series, the Long Island groups are found to be consistently higher than the corresponding groups in the other two. The

TABLE I. THE INCIDENCE OF VALVULAR LESIONS IN THREE AUTOPSY SERIES

VALVE INVOLVED	AUTOPSY SERIES*	ACUTE OR MILD LESIONS						STENOTIC LESIONS					
		MALE		FEMALE		TOTAL		MALE		FEMALE		TOTAL	
		NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Group 1: mitral damaged; aortic normal	L. I.	30	(1.27)	54	(3.34)	84	(2.11)	20	(0.85)	65	(4.02)	85	(2.14)
	B. H.	34	(1.09)	9	(0.73)	43	(0.98)	21	(0.67)	32	(2.59)	53	(1.21)
	C. R.	13	(0.52)	28	(1.66)	41	(0.98)	23	(0.91)	25	(1.48)	48	(1.14)
Group 2: both mitral and aortic damaged	L. I.	39	(1.65)	19	(1.18)	58	(1.46)	83	(3.52)	52	(3.22)	135	(3.40)
	B. H.	27	(0.86)	20	(1.62)	47	(1.08)	61	(1.95)	44	(3.56)	105	(2.40)
	C. R.	6	(0.24)	9	(0.53)	15	(0.36)	25	(0.99)	7	(0.41)	32	(0.76)
Groups 1 and 2 combined	L. I.	69	(2.92)	73	(4.52)	142	(3.57)	103	(4.36)	117	(7.24)	220	(5.53)
	B. H.	61	(1.95)	29	(2.35)	90	(2.06)	82	(2.62)	76	(6.15)	158	(3.61)
	C. R.	19	(0.76)	37	(2.19)	56	(1.33)	48	(1.91)	32	(1.89)	80	(1.90)
Group 3: aortic damaged; mitral normal	L. I.	25	(1.06)	12	(0.74)	37	(0.96)	42	(1.78)	6	(0.37)	48	(1.20)
	B. H.	15	(0.48)	6	(0.49)	21	(0.47)	42	(1.34)	12	(0.97)	54	(1.24)
	C. R.	9	(0.36)	2	(0.12)	11	(0.26)	19	(0.75)	3	(0.18)	22	(0.52)

*L.I., Long Island series.
B.H., Bellevue Hospital series.
C.R., Costa Rican series.

Bellevue groups occupy an intermediate position in all but two categories. The Costa Rican series has a slightly higher incidence than the Bellevue series of stenotic lesions of the mitral valve in males and of acute and mild lesions of the mitral valve in females. The constancy of the relative incidence of rheumatic valvular lesions in the three series is more apparent when all types are grouped together. There are about three times as many examples of rheumatic endocarditis in the Long Island series as in the Costa Rican, and about twice as many in the Bellevue series as in the Costa Rican. One noteworthy variable finding is observed when the incidence of various types of rheumatic valvular lesions in the three series is compared, namely in the Costa Rican series a relatively small proportion have rheumatic involvement of both mitral and aortic valves.

The differences in incidence of rheumatic lesions do not necessarily reflect differences in the incidence of the disease in the entire populations from which these three hospitals receive patients. Both the Bellevue and Long Island hospitals serve essentially the same type of persons and yet show marked differences in the incidence of rheumatic lesions. This indicates that the smaller incidence in the Costa Rican series is not necessarily the result of decreased susceptibility of the Costa Rican population as a whole because of environmental or racial backgrounds. The hospital San Juan de Dios receives patients from both inland mountainous areas and costal lowland areas. The incidence of rheumatic disease in these two regions may vary greatly. However, the finding that the mitral valve alone is involved in a relatively high percentage of the Costa Rican cases does suggest that rheumatic heart disease tends to run a milder course in that country. Another equally valid explanation to account for this difference may be offered. Because of the prevalence of tuberculosis, malnutrition, and helminthic and protozoal diseases, rheumatic patients in Costa Rica may die at a relatively young age before the rheumatic lesions have progressed to advanced stages. In the Costa Rican series 51.1 per cent of the males and 62.6 per cent of the females were between 10 and 50 years of age at death. The corresponding age period in the Bellevue series contained only 28.4 per cent males and 34 per cent females. In the Long Island series there were 29.4

per cent males and 32.1 per cent females in this age period. No very satisfactory explanation can be offered to account for the differences in incidence of rheumatic lesions between the Bellevue and Long Island series. It is possible, however, that the Long Island College Hospital, and even the Kings County Hospital, treat patients of a somewhat higher economic level than does Bellevue Hospital.

In the male groups in which only the aortic valve was calcified, the three series show the same order of frequency as do the groups with definite rheumatic lesions. The Long Island series has the highest percentages; the Bellevue series is second; and the Costa Rican is third. A striking preponderance of calcareous aortic stenosis in the male is noted in all three series. This is in accord with the sex incidence of this lesion as reported in most published series. Of the 1,615 females in the Long Island group only six had calcareous aortic stenosis, and of the 1,691 females in the Costa Rican series only three had this lesion. The number of females with calcareous aortic stenosis in these two series is so small that percentages obtained from it are obviously without statistical value. Therefore the finding of a higher incidence of aortic stenosis among females in the Bellevue series over that in the other two, as shown in Table I, is probably a chance variation. As noted in most published analyses on the incidence of calcareous aortic stenosis, an older age group is involved than is the case with the accepted rheumatic types of lesions. The median age for the groups of aortic stenosis is as follows: in the Long Island series, males 64 years, females 67 years; in the Bellevue series, males 67 years, females 66 years; and, in the Costa Rican series, males 47 years, females 60 years. If all the definite rheumatic lesions in which one or more valves were stenotic are grouped together, the following median ages for the three series are obtained: Long Island series, males 40 years, females 41 years; Bellevue series, males 50 years, females 47 years; Costa Rican series, males 44 years, females 37 years.

It is thus seen that certain features of both the rheumatic groups and the groups with only aortic valve involvement are constant in all three series. This may be taken as evidence that the lesions of rheumatic disease follow a fairly fixed pattern in different populations and in these two different parts of the world. It is therefore reasonable to expect that, if calcareous aortic stenosis is rheumatic in origin, its incidence should bear some fixed relation to the incidence of other rheumatic lesions.

In Table II the incidence of the various types of valvular lesions is compared in the three autopsy series. All acute, mild, and stenotic lesions of the mitral valve alone, and of both mitral and aortic valves, are grouped together for males, and for both males and females in each series. Similarly, all acute, mild, and stenotic lesions involving only the aortic valve are grouped together for males and for males and females. The ratios between the two corresponding groups of males in each series are extremely constant. There are about two and one-half times as many cases with established types of rheumatic lesions as with lesions limited to the aortic valve in each series. In other words, in series showing a high incidence of rheumatic endocarditis, the incidence of calcareous aortic stenosis is correspondingly high and vice versa.

A very small number of cases of acute verrucous endocarditis limited to the aortic valve is included in each series. These showed the characteristic inflammatory changes of rheumatic endocarditis. If calcareous aortic stenosis is rheumatic in origin, then this acute lesion probably represents an early stage of the lesion. In comparing the incidence of calcareous lesions of the aortic valve alone to definite rheumatic lesions in which the mitral valve is involved, it

TABLE II. THE RELATIVE INCIDENCE OF LESIONS OF THE AORTIC VALVE (MITRAL VALVE UNDAMAGED) AND OTHER VALVULAR LESIONS IN THREE AUTOPSY SERIES

	AORTIC LESIONS (MITRAL UNDAMAGED)				OTHER VALVULAR‡ LESIONS		RATIO OF OTHER VALVULAR LESIONS TO CALCAREOUS AORTIC LESIONS	RATIO OF OTHER VALVULAR LESIONS TO TOTAL AORTIC LESIONS
	CALCAREOUS* DEFORMITY		TOTAL†					
	NO.	%	NO.	%	NO.	%		
				Males				
Long Island	60	(2.58)	67	(2.84)	172	(7.29)	2.8:1	2.6:1
Bellevue	56	(1.78)	57	(1.82)	143	(4.57)	2.6:1	2.5:1
Costa Rica	23	(0.90)	28	(1.11)	67	(2.67)	3.0:1	2.4:1
				Total (Males and Females)				
Long Island	73	(1.84)	85	(2.15)	362	(9.10)	4.9:1	4.2:1
Bellevue	74	(1.69)	75	(1.71)	248	(5.68)	3.4:1	3.3:1
Costa Rica	26	(0.62)	33	(0.78)	136	(3.23)	5.2:1	4.1:1

*Includes all calcareous deforming lesions of aortic valve; acute verrucous lesions excluded.

†Includes all acute, mild, and stenotic lesions of the aortic valve.

‡Includes all acute, mild, and stenotic lesions of mitral valve alone and of both mitral and aortic valve.

becomes a moot question whether acute verrucous aortic lesions should be included or excluded. However, the number of these cases is so small that their exclusion does not significantly alter the ratio between the incidence of calcareous lesions of the aortic valve and all other definite types of rheumatic valvular disease (Table II).

As noted previously, the incidence of calcareous aortic stenosis in females is so low that the relatively small groups analyzed do not provide enough examples to give constant percentage values. In the Long Island group of eighteen females with lesions limited to the aortic valve, five showed acute verrucous endocarditis, seven had mild deformities with aortic insufficiency, and only six were stenotic. Of the five females with lesions limited to the aortic valve in the Costa Rican series, two showed acute verrucous endocarditis, and three were stenotic. Because of the small number of females with aortic stenosis in these two series their ratios are not shown in the table. When males and females are grouped together, the ratio of rheumatic endocarditis to the aortic lesions is increased because of the low incidence of aortic lesions in females. The ratios of the Long Island and Costa Rican group are still constant. The ratio of the Bellevue group is slightly lower, but this discrepancy is probably without significance. These findings suggest that the mechanisms involved in the production of aortic valve lesions alone and of recognized types of rheumatic valvular lesions are probably fundamentally the same.

It is, of course, quite possible that the close relationship between the incidence of aortic valve lesions alone, and other types of rheumatic endocarditis, is coincidental. As noted above, a high percentage of the patients in the Costa Rican series died before the age of 50 years. It was also noted that calcareous aortic stenosis occurs most frequently in advanced age groups. It is therefore possible that the low incidence of calcareous aortic stenosis in the Costa Rican series is not related to the low incidence of rheumatic disease, but rather to the short survival period. In Table III the incidence of calcareous aortic stenosis is shown in the groups of persons dying at an older age than 50 years in each of the three series. Even in these older age groups, the Long Island series has the highest incidence of aortic lesions. The Bellevue series is second, and the Costa Rican is third. In males, the ratio between the three series is approximately 3:2:1. This is about the same relative incidence of all accepted rheumatic valvular lesions in the three series (Table I). When females who died after they had reached the age of 50 years are included, the incidence of aortic lesions

in the Bellevue series approximates that in the Long Island group. As already pointed out, this is probably because the incidence of aortic stenosis in this sex is so low that accidental variation plays a role in the small number of females included in the analysis. Even here, however, the Costa Rican series has only one-half as many examples of aortic lesions as do the other two series. It is obvious therefore that the low incidence of aortic lesions in the Costa Rican series is independent of age.

TABLE III. THE INCIDENCE OF LESIONS OF THE AORTIC VALVE (MITRAL VALVE UNDAMAGED) IN GROUPS OF PATIENTS OVER 50 YEARS OF AGE IN THREE AUTOPSY SERIES

	TOTAL	NUMBER WITH LESIONS	PERCENTAGE
		Males	
Long Island	1,378	41	3.0
Bellevue	2,168	39	1.8
Costa Rica	885	11	1.2
		Males and Females	
Long Island	2,234	46	2.1
Bellevue	2,908	56	1.9
Costa Rica	1,254	13	1.0

SUMMARY

The incidence of rheumatic endocarditis of the mitral valve alone, and of the mitral and aortic valves together, in three independent series of autopsies is compared. Differences in the total incidence of valvular lesions were noted in each of the three series. These differences cannot be attributed to racial or geographical factors alone, since two of the series represent cases from essentially the same types of population in the New York area. However, the relative incidence of each type of valve lesion is constant in the three series. Mitral stenosis is more common in women than in men in each series. The incidence of calcareous deforming lesions, limited to the aortic valve, is also determined in the three autopsy series and is found to vary constantly with the incidence of rheumatic lesions in each of the three series. In males, lesions of the mitral valve alone, together with lesions of both mitral and aortic valves, are about two and one-half to three times as common in each series as are calcareous deforming lesions limited to the aortic valve. Lesions of the aortic valve only are more common in males and involve an older age group than do the other types of rheumatic lesions. The incidence of lesions of the aortic valve only, in the groups surviving longer than 50 years in each series, is relatively the same as for the entire age group in each series, however.

CONCLUSION

The constant ratio of the incidence of calcareous aortic stenosis to the incidence of accepted types of rheumatic endocarditis suggests that the two lesions have a common etiology.

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THE ELECTROCARDIOGRAM IN PNEUMOPERITONEUM

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CLINICAL OBSERVATIONS

THE introduction of pneumoperitoneum on a larger scale in the treatment of pulmonary tuberculosis[1] has made it possible to study the effect of a markedly raised diaphragm on the heart and circulation. Two outstanding features emerge from the observations. First, cardiovascular distress seldom occurs in such patients, even if one side of the diaphragm rises as high as the second rib anteriorly. Second, an electrocardiogram is obtained which resembles the pattern of acute cor pulmonale.[2] In this paper both these observations will be supplemented by further investigations of the vital capacity and of a detailed electrocardiographic analysis with an attempt to derive from the findings the geometric displacement of the heart.

Several hundred pneumoperitonea have been induced during the last three years at Clare Hall Hospital, and only one case is known in which the patient, who suffered from extensive bilateral tuberculosis with cavitation and was, in fact, in a hopeless condition, developed edema, cyanosis, and breathlessness. Whether this clinical picture can be ascribed to the mere displacement of the heart following the elevation of the diaphragm or to a failing myocardium as a sequela of tuberculous toxemia remains undecided. Attacks of transient breath-

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lessness do occur following the induction of pneumoperitoneum or after the first three or four refills, but these have been of moderate degree, never causing distress, and have disappeared as the refills went on in the ensuing weeks. They often appear more conspicuously when abdominal adhesions are present and when the initial slight abdominal discomfort prevents the patient from breathing as freely as he usually does later on. It seems at this juncture advisable to emphasize that the technique employed in this hospital aims at the *gradual* rise of the diaphragm previously paralyzed by phrenic crush. A sudden marked elevation of the diaphragm is liable to cause distress. The technique, first applied extensively in England by Clifford-Jones and Macdonald,[1] follows.

TECHNIQUE

The patients dealt with in this paper had a phrenic crush performed on one side three to four weeks before the induction of the pneumoperitoneum. No premedication was given before the induction. The patient lay comfortably in the recumbent position. The skin was injected with a local anesthetic about 1 inch below the left costal margin. A dry medium-sized or long-sized Morland A-P refill needle, which was connected with the open manometer of an A-P box, was pushed slowly through the abdominal wall and the peritoneum. The passing of the needle through the peritoneum was usually marked by a click, and the manometer might show a sudden movement. Usually no pressure was recorded until air had been introduced. Air was run in slowly, and the pressure was checked. Under frequent control of pressure, 600 to 1,000 c.c. were then

TABLE I

DATE	TREATMENT	VITAL CAPACITY IN C.C. OF AIR, BEFORE REFILL	REFILL IN C.C. OF AIR	VITAL CAPACITY IN C.C. OF AIR, AFTER REFILL
6/4/44	Phrenic crush (R)			
11/3/44		*2,500*		
15/3/44	Induction of P.P.			
21/3/44		2,500	1,400 (+3+5)*	2,700
29/3/44		3,000	1,000 (+5+10)	2,900
5/4/44		2,900	1,200 (+7+14)	2,700
12/4/44		3,000	900 (+11+8)	2,700
19/4/44		3,000	1,000 (+17+11)	2,800
26/4/44		*3,000*	1,000 (+6+10)	3,100

This table shows some rise of the vital capacity figures after a period of six weeks' treatment.

*The figures in parentheses indicate the initial and the final intra-abdominal pressures in centimeters of water.

TABLE II

DATE	TREATMENT	VITAL CAPACITY IN C.C. OF AIR BEFORE REFILL	REFILL IN C.C. OF AIR	VITAL CAPACITY IN C.C. OF AIR AFTER REFILL
13/1/44	Phrenic crush (L)			
10/2/44		*3,200*		
10/2/44	Induction of P.P.			
15/2/44		3,000	1,100 (+8+11)*	3,000
22/2/44		3,100	1,000 (+9+12)	3,500
7/3/44		3,300	1,500 (+10+10)	3,100
14/3/44		3,100	1,400 (+9+11)	2,700
21/3/44		3,100	1,400 (+7+15)	3,000
29/3/44		–	1,000 (+15+16)	–
5/4/44		–	1,200 (+14+12)	3,200
12/4/44		3,400	800 (+10+12)	3,100
19/4/44		3,200	800 (+8+9)	3,000
26/4/44		*3,200*	1,000 (+8+10)	3,100

This table shows no change of the vital capacity after a period of more than two months' treatment. The left diaphragm was markedly raised.

*The figures in parentheses indicate the initial and the final intra-abdominal pressures in centimeters of water.

introduced. No definite ruling as to the final pressure can be given; +8 or +10 cm. of water was a common finding, but it sometimes rose as high as +25 cm. when adhesions were present. To ascertain the rise of the diaphragm the patient was fluoroscoped immediately after the induction. The first refill of about 800 c.c. was given a day or two after the induction, and one more refill was given on the third or fourth day, according to the elevation of the diaphragm. As soon as an adequate rise was established, weekly refills of 800 to 1,200 c.c. were given.

VITAL CAPACITY

In order to find an answer to the surprising lack of dyspnea, the vital capacity was measured in a number of cases, some of which are shown in Tables I, II, III, IV, and V. In addition, a larger number of cases have been summarized in a curve (Fig. 1). All points in this graph were obtained by dividing the estimated vital capacity by the initial vital capacity figure in each instance, thus making all the data for the different patients comparable with one another.

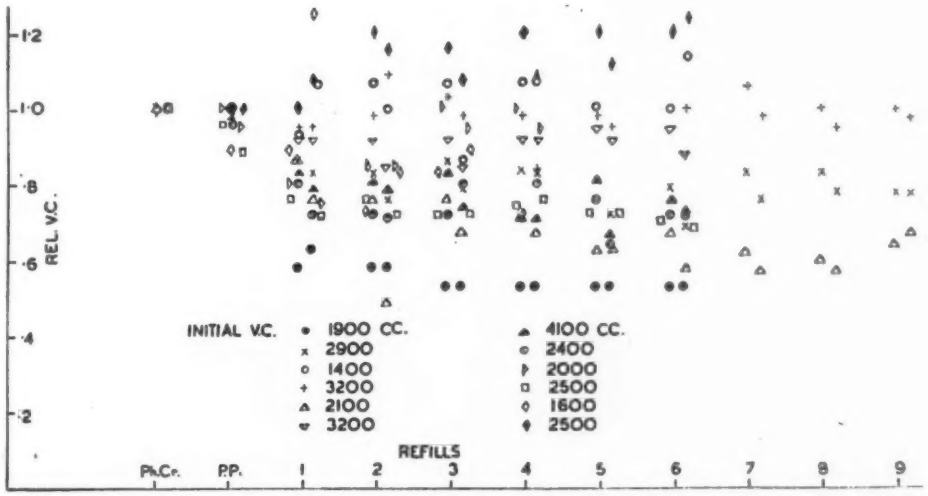


Fig. 1.—Relative vital capacities of twelve cases at various stages of the treatment. The relative vital capacity is the measured capacity divided by the initial capacity. *Ph.Cr.* indicates phrenic crush; *P.P.*, indicates induction of pneumoperitoneum.

The conclusion we have drawn from these data is that they do not show a uniform trend. In several cases, after a series of refills, no marked decrease of the vital capacity was noted; some even showed a slight increase and, in very few of the cases showing a drop, was the vital capacity grossly affected.

TABLE III

DATE	TREATMENT	VITAL CAPACITY IN C.C. OF AIR BEFORE REFILL	REFILL IN C.C. OF AIR	VITAL CAPACITY IN C.C. OF AIR AFTER REFILL
18/2/44	Phrenic crush (R)			
15/3/44	Induction of P.P.	*3,200*	1,000 (+1+5)*	
21/3/44		2,900	1,200 (+5+11)	2,900
29/3/44		2,900	1,000 (+7+14)	2,700
5/4/44		2,900	1,000 (+8+12)	2,700
12/4/44		2,900	1,000 (+9+13)	2,900
19/4/44		3,000	1,000 (+7+9)	2,900
26/4/44		*3,000*	900 (+7+8)	2,800

This table shows hardly any change of the vital capacity during the period of six weeks. A single refill of 1,000 c.c. affected the vital capacity only slightly.

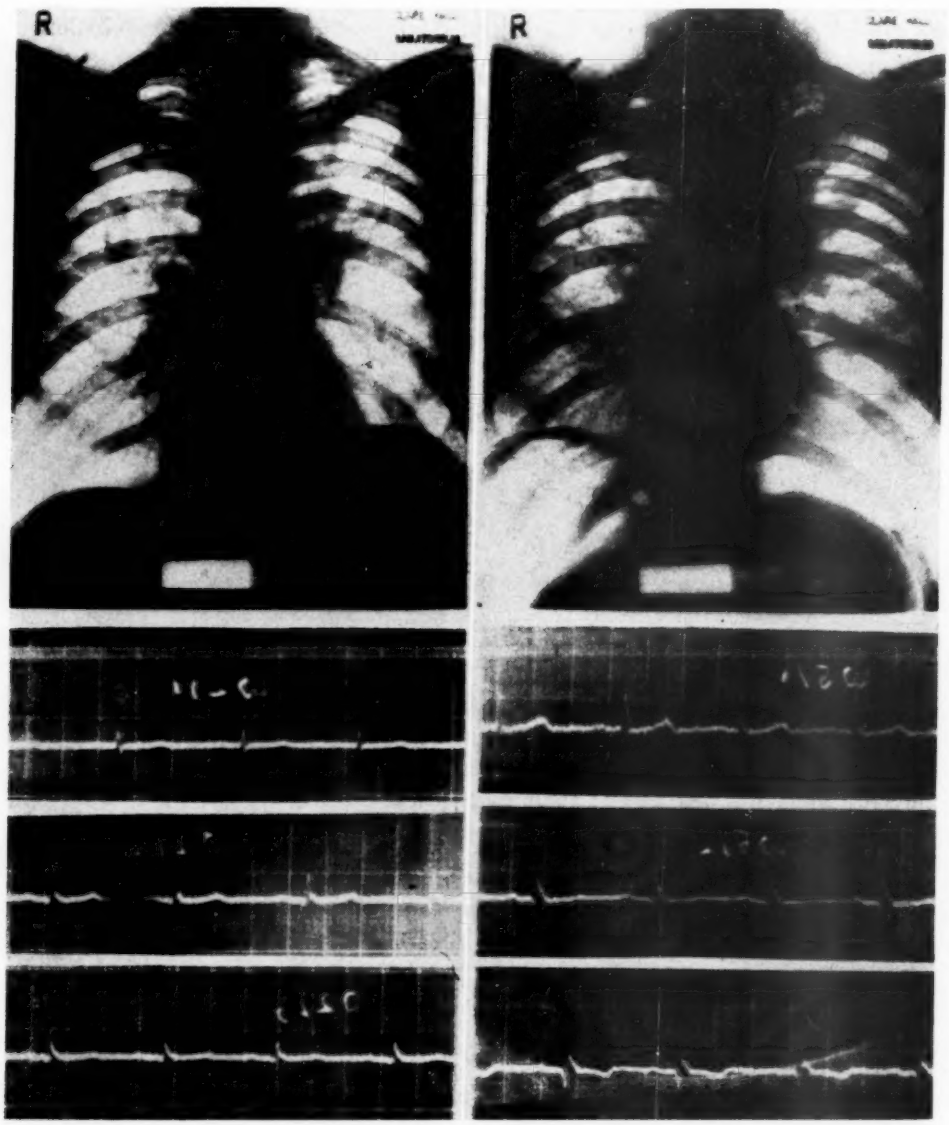
*The figures in parentheses indicate the initial and the final intra-abdominal pressures in centimeters of water.

TABLE IV

DATE	TREATMENT	VITAL CAPACITY IN C.C. OF AIR BEFORE REFILL	REFILL IN C.C. OF AIR	VITAL CAPACITY IN C.C. OF AIR AFTER REFILL
29/2/44	Phrenic crush (L)			
11/3/44		*4,100*		
21/3/44	Induction of P.P.	3,500	1,200 (+6+8)*	3,300
29/3/44		3,400	1,000 (+5+7)	3,300
5/4/44		3,500	1,200 (+4+10)	3,100
12/4/44		3,500	900 (+4+7)	3,000
19/4/44		3,400	800 (+4+7)	2,800
26/4/44		*3,200*	800 (+5+7)	3,100

This table shows an initial decrease of the vital capacity of 600 cubic centimeters. After this there was no further marked change. The vital capacity remained high.

*The figures in parentheses indicate the initial and the final intra-abdominal pressures in centimeters of water.



A. *B.*

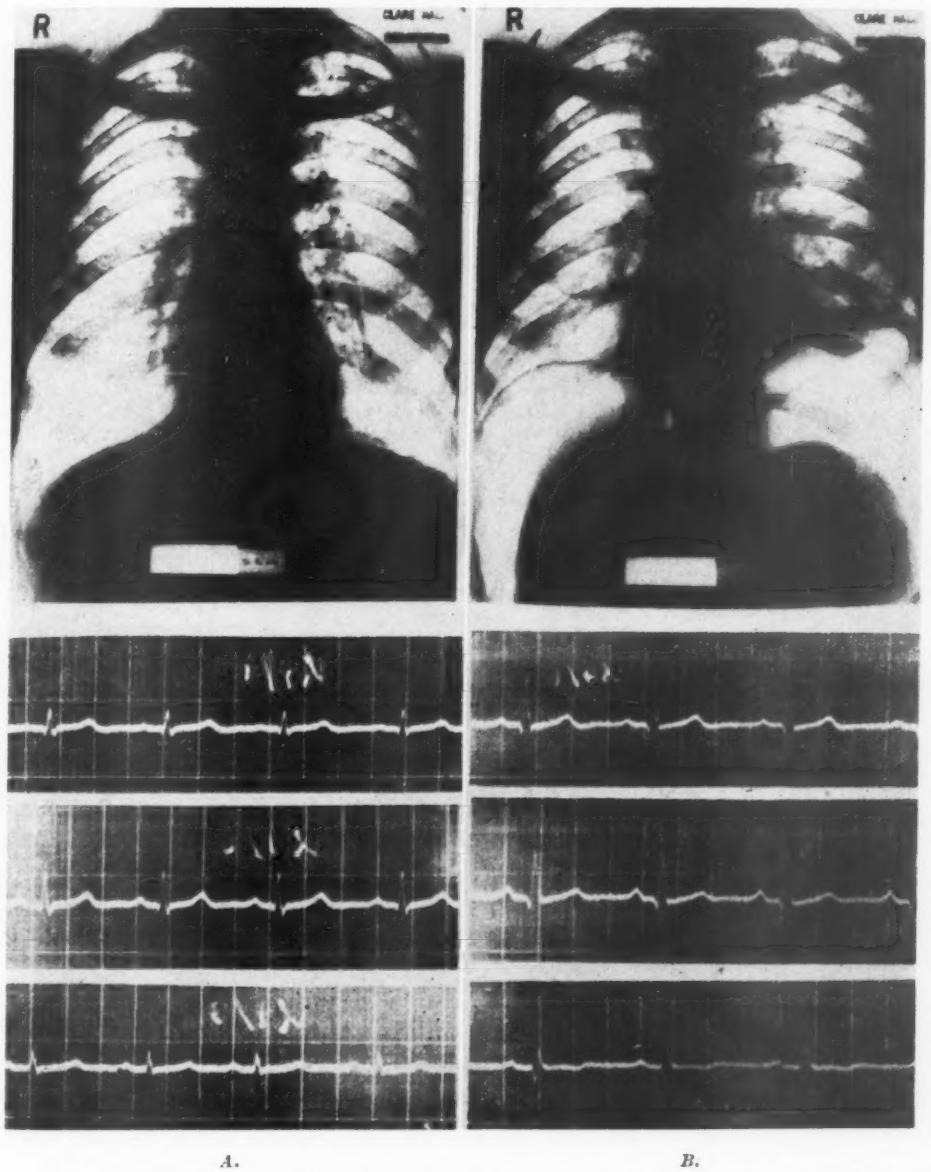
Fig. 2.—H. W.: *A*, Slight left diaphragmatic rise after left phrenic crush. *B*, During pneumoperitoneum treatment. Marked rise of the left paralyzed diaphragm. Some rise of the right diaphragm. The electrocardiogram shows some flattening of S-T_2, a conspicuous Q_3, and T_3 inverted.

TABLE V

DATE	TREATMENT	VITAL CAPACITY IN C.C. OF AIR BEFORE REFILL	REFILL IN C.C. OF AIR	VITAL CAPACITY IN C.C. OF AIR AFTER REFILL
18/2/44	Phrenic crush (L)			
14/3/44	Induction of P.P.	*2,400*	1,000 (+1+6)*	2,200
20/3/33		1,900	1,400 (+8+11)	1,800
27/3/44		1,900	1,400 (+7+10)	1,800
3/4/44		1,800	1,000 (+6+9)	1,800
11/4/44		1,850	800 (+7)	1,900
17/4/44		1,800	900 (+6+9)	1,800
24/4/44		*1,750*	800 (+5+7)	1,700

This table shows an appreciable decrease of the vital capacity in a period of six weeks' treatment.

*The figures in parentheses indicate the initial and the final intra-abdominal pressures in centimeters of water.

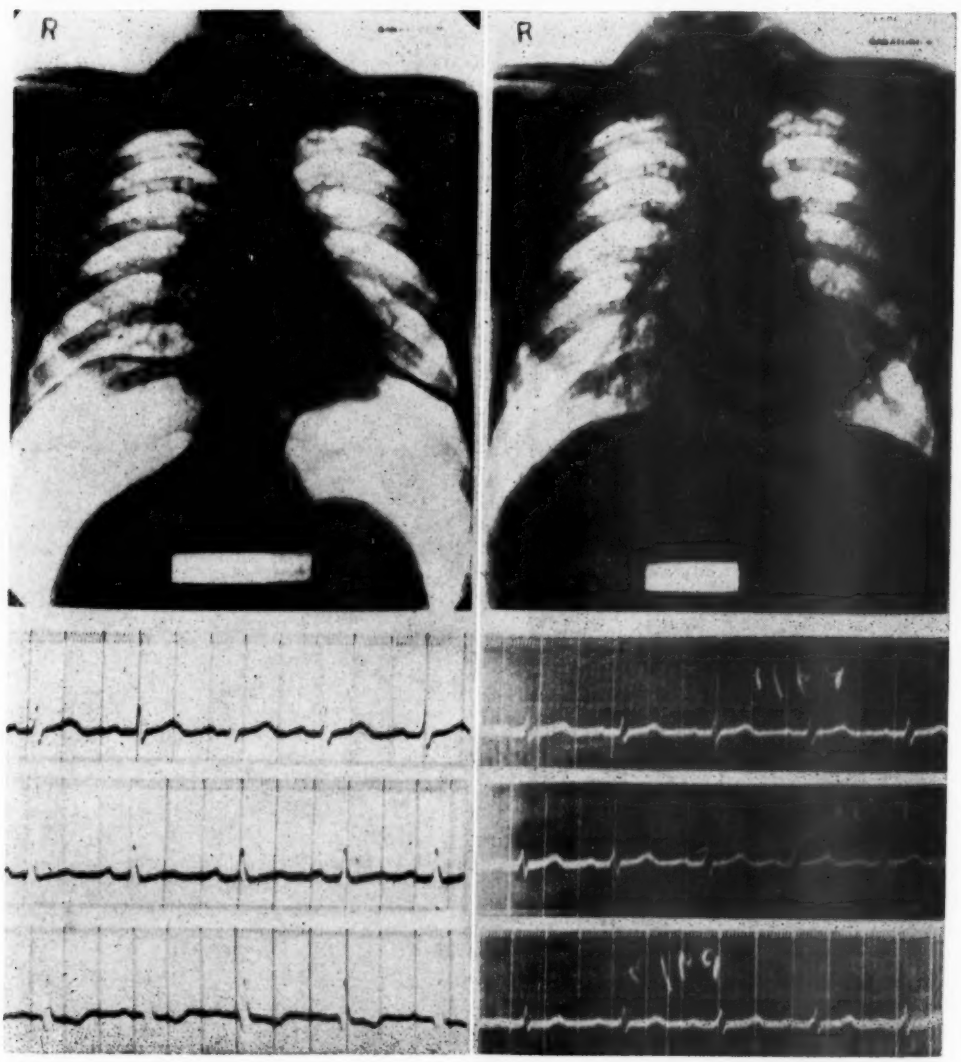


A. *B.*

Fig. 3.—K. T.: *A*, Before left phrenic crush. *B*, During treatment with pneumoperitoneum. Both sides of the diaphragm raised; the left more than the right. Electrocardiogram: S-T_2 becomes slightly flatter; Q_3 is conspicuous, and T_3 is inverted.

ELECTROCARDIOGRAPHIC PATTERN

The electrocardiographic pattern is characterized by the following features: Soon after the rise of the diaphragm, whether it be the right side, the left side, or both, the S-T segment in Lead II flattens. In Lead III a conspicuous Q wave followed by a small R and an inverted T deflection occurs. This is an almost constant picture, the only variations being that these characteristics may be more or less pronounced. Typical examples are shown in Figs. 2, 4, and 5. Figs. 2 and 3 illustrate the condition before the induction and after a number of refills. In Fig. 4 the first electrocardiogram (*A*) was taken at the height of the diaphragmatic rise and exhibits all the features described. Then the pneumoperitoneum was abandoned, and the second tracing (*B*) was taken after the diaphragm had descended. The pattern has become normal again. Fig. 5 is of a patient who showed a typical pneumoperitoneum pattern as the diaphragm

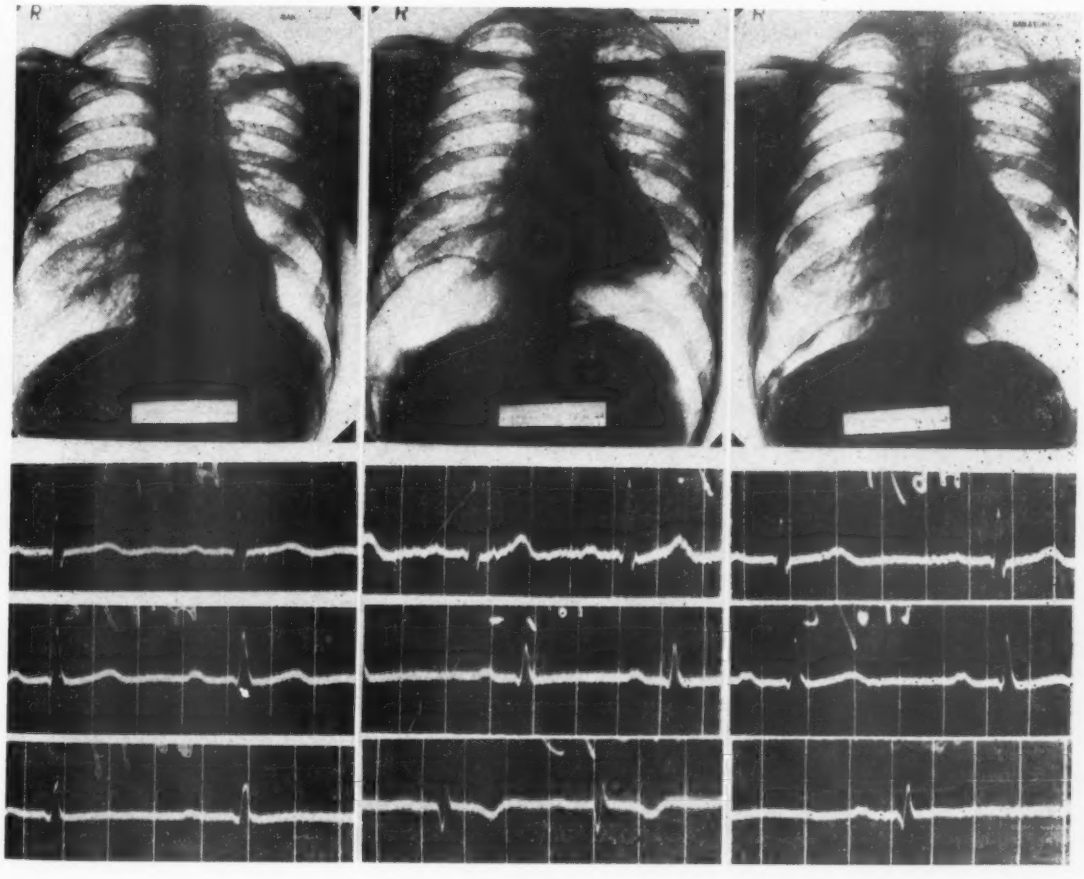


A. *B.*

Fig. 4.—A. P.: *A*, **X-ray and electrocardiogram at the height of the diaphragmatic rise. S-T_3 is flattened, Q_3 is present, and T_3 is inverted.** *B*, **Pneumoperitoneum abandoned. The diaphragm has descended to its lowest level. The electrocardiogram now shows a normal S-T_3 and S-T_2. No Q_3 is present.**

rose; then the refills were discontinued, the diaphragm came down, and with it the electrocardiogram approached the normal, though not completely, as the phrenic paralysis persisted and the diaphragm did not descend to its lowest level.

The electrocardiograms as demonstrated here represent only the initial and final patterns. The characteristic picture usually occurs soon after the early refills.



A. *B.* *C.*

Fig. 5.—J. H.: *A*, Left diaphragm is slightly raised after left phrenic crush. *B*, During treatment with pneumoperitoneum both sides of diaphragm raised; left higher than the right. The electrocardiogram shows flattening of S-T_3, marked Q_3, and inverted T_3. *C*, Pneumoperitoneum abandoned; diaphragm approaching previous level. Electrocardiogram: T_3 reappears, Q_3 becomes smaller, and R_3 taller. The inversion of T_3 has disappeared.

DISCUSSION

The electrocardiograms characteristic of pneumoperitoneum resemble to a certain extent the Q_3-T_3 pattern of coronary thrombosis involving the posterior wall, although with pneumoperitoneum we do not find that the S-T segment in Lead III ever becomes really dome-shaped. No clinical symptoms, however, suggesting coronary thrombosis have been noted. Moreover, no clinical signs such as anterior thoracic pain, fainting attacks, or sudden onset of dyspnea have been recorded. Therefore, the suggestion that these electrocardiograms represent the pattern of acute cor pulmonale due to pulmonary embolism, can be dismissed. However, it is conceivable that a reduction of the bed of the pul-

monary circulation is brought about by the elevation of the diaphragm, thus straining the right heart. This seems unlikely for the following reasons. First, the vital capacity—an important though not the sole measure of pulmonary function—does not show any gross diminution; sometimes even a slight rise occurs. Second, in collapse therapy, such as artificial pneumothorax after adhesion section, or after a nine-rib thoracoplasty, much larger areas than those affected by pneumoperitoneum are usually collapsed without the electrocardiogram, even approaching the pneumoperitoneum pattern as described previously. Right axis deviation with a deep S deflection in Lead I is often one of the findings when the heart is displaced by these collapse measures. Third, the pattern obtained with a raised diaphragm is reversible, and can be brought back to normal with the descent of the diaphragm.

It thus appears that we have exhausted all the known clinical possibilities of accounting for the electrocardiographic changes observed. The only explanation left is to assume that the heart remains functionally intact and that the changes in the electrocardiogram are brought about merely by a geometric displacement of the heart. The tracings were therefore analyzed from this point of view.

METHOD OF ANALYSIS

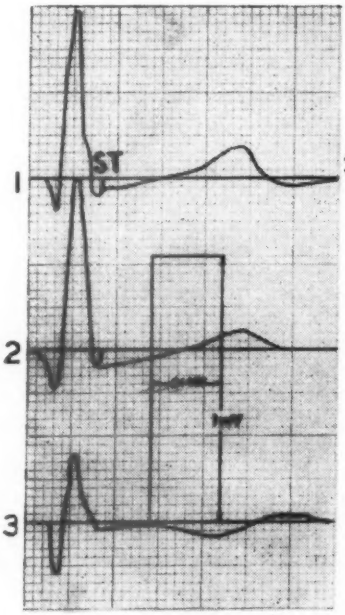
For the purpose of the present analysis it is assumed that an electrical axis determination is equivalent to a determination of the geometric position of the heart. Thus, the electrical axes are used as pointers fixed to the heart, following and indicating its displacements. Some of the changes could be studied from the alteration of the heart's position in the roentgenogram, but the measurements are not reliable. The electrical methods, however, were found to convey a more detailed picture of its movements in three dimensions.

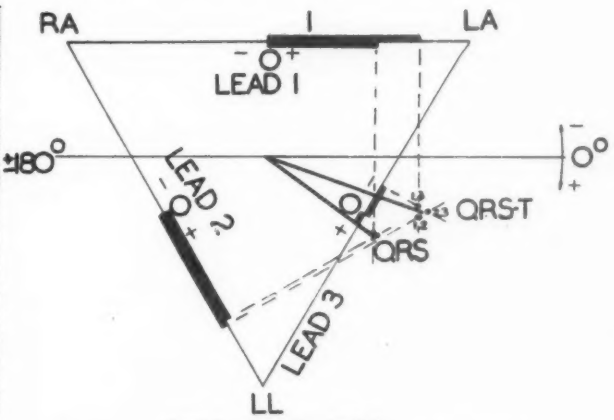
Two major difficulties had to be overcome before electrical axis determinations could be carried out. One of these, the fact that the instrument available could only record a single lead at a time, was purely technical. All published methods of electrical axis determination are based on the simultaneous recording of at least two of the standard leads; from these two tracings the position of the electrical axis in the frontal plane at any chosen instant can be worked out by one of several well-established methods. The second difficulty is more fundamental. As we wish to correlate the displacement of the electrical vector with that of the heart itself, it is necessary to carry out the axis determination at a well-defined point of the heart cycle. However, the very change in the electrocardiographic pattern we are interested in makes it impossible to recognize with any certainty the phases of the cycle before and after the displacement of the heart. This second difficulty would persist even if it were possible to record two leads simultaneously.

The application of a concept introduced by Wilson, MacLeod, Barker, and Johnston,[3] and used very extensively since by Ashman, Byer, and Bayley[4] offered a way out of both these difficulties. These authors have defined as the "ventricular gradient" and the "QRS vector" a pair of electrical axes which represent the total average activity of the whole ventricular complex and of the QRS complex respectively. The averaging process here refers both to the direction and the intensity of the individual vectors making up the electrical activity of the heart. As a result of the calculation we obtain new vectors of which we know both the direction and the magnitude (length), the latter being designated as manifest value. Being averages over the whole or a well-defined

part of the QRS-T complex, these vectors are not tied to any particular phase and can therefore be used as indicators to denote any changes in the position of the heart. Ashman and Byer[4] may have had an application such as this in mind when they correlated the direction of the average vectors with the position of normal human hearts, although the method has apparently not been applied to cases where the position was actually changed in the same patient.

Details of the method used are not of great interest. Suffice it to say that the electrocardiograms were projected on graph paper and the outlines were drawn. The areas under the enlarged electrocardiograms so obtained were determined by counting those squares above the zero line as positive, and those below as negative. The sum of the squares counted for any one of the leads (averaging in each case over three cycles) represents the component of the average vector in the direction given by the points at which the lead was taken.





	Lead 1	Lead 2	Lead 3
Q	- 3.2	- 6.5	- 7.0
R	+37.5	+43.0	+10.5
S	- 2.5	- 1.5	0
T	- 5.0	-10.5	-16.0
	+19.5	+12.5	+ 3.0
	- 3.5		
QRS	+31.8	+35.0	+ 3.5
QRS-T	+42.8	+37.0	- 9.5
QRS/2.48	+12.5	+14.1	+ 1.4
QRS-T/2.48	+17.3	+14.9	- 3.8

Calibration
0.1 mv sec = 248
1 μv sec = 2.48

Resultant
37° 15.5 μv sec
30° 16.9 μv sec

Fig. 6.—Illustrating method of evaluation. The areas under the different parts of the electrocardiographic tracings are tabulated and added to give those of QRS and QRS-T. The latter divided by the area occupied by 1 μv second gives the components of the average vectors along the sides of the Einthoven triangle. These components are marked by heavy lines inside the triangle for QRS and outside the triangle for QRS-T. The resultant vectors are constructed from their components as shown; their lengths and directions are read off the diagram. Where the three values of the resultant vector (marked *1/2, 2/3, 1/3*) differ, the center of the little triangle formed is the average of the three values given in the table. The figure also illustrates the choice of the demarcation between S and T.

An example of the procedure is given in Fig. 6. The areas measured were standardized by the deflection produced by impressing the usual calibration voltage of 1 millivolt on the recording galvanometer; knowledge of the standardized deflection and of the time scale recorded in each case enables one to express these areas in terms of millivolt-seconds (mv) or microvolt-seconds (μv). The directions of the vectors were determined by using the chart of Carter, Richter, and Greene.[5] Measurements of the values in any of the two leads allow the determination of the direction and the manifest value of an electric heart axis as projected on to the frontal plane; here all three leads were utilized in order to check the validity of the Einthoven triangle. In this way three values were obtained in each case, the averages of which are quoted in Table VI. All the values are tabulated for all measurements from one of the patients, in order to

convey an idea of the accuracy obtainable. It is considered that the agreement of the values justifies the method adopted for evaluating the electrocardiograms; but it should be pointed out that the accuracy is lower for patients with lower voltages in their electrocardiograms.

INTERPRETATION AND RESULTS

When one attempts to determine the QRS vector a difficulty of interpretation arises which is probably less pronounced with a normal human heart than with the displaced heart under consideration. The displacement of the heart manifests itself by a strong deviation of the S-T segment from the zero line, in particular in Lead III. This means that if the definition given by Ashman and Byer[4] ("the area of S is the area below the upper edge of the S-T junction, or, if that junction is deviated, below the level of the base line . . .") is followed literally, misleading results will be obtained; the QRS complex would seem to last very much longer in one of the leads than in the other two. Since there is no systematic method of deciding where the QRS complex finishes and the T wave begins it was often necessary to make an arbitrary decision. Fig. 6 illustrates a possible choice; the S deflection is regarded as terminating at the point where the clockwise curvature of the deflection toward the horizontal is strongest. A

TABLE VI

STAGE IN TREATMENT		LEADS	QRS ANGLE (°)	QRS MAN. VAL. (μV SEC.)	QRS-T ANGLE (°)	QRS-T MAN. VAL. (μV SEC.)	X-RAY ANGLE (°)
J. H.	B.	1/2	58	15.2	45	19.6	52
		2/3	68	15.2	52	19.3	
		3/1	62.5	17.4	49	21.8	
		av.	62	15.8	48	20.1	
	P. P.	1/2	29	13.4	+ 9.5	22.8	39
		2/3	26	14.5	+ 2	22.8	
		3/1	25.5	13.0	- 4	26.7	
		av.	27	13.4	+ 2	24.0	
	Ref.	1/2	0	9.6	-17	15.2	38
		2/3	+14	7.1	-14	10.6	
		3/1	+19.5	10.3	- 4.5	13.9	
		av.	+10	8.9	-11	13.0	
	P.a.	1/2	43.5	13.9	39	20.4	44
		2/3	57	13.3	47	19.4	
		3/1	51.5	16.1	45	21.8	
		av.	51	14.5	43	20.5	
A. P.	Ref.		71	6.3	12	17.2	45
	Ref.		64	10.7	6	15.2	--
	P.a.		73	7.4	55	18.3	43
	P.a.		91	4.7	64	20.5	58
	P.a.		90	5.2	45	22.4	--
	P.a.		80	3.5	62	15.3	52
E. A.	B.		71	5.9	28	8.5	65
	Ref.		39	10.1	-17	11.9	--
	Ref.		30	9.0	-21	8.5	62
	Ref.		53	7.0	11	6.0	53
H. W.	B.		74	7.0	65	15.3	55
	Ph. Cr.		71	6.3	69	10.1	--
	Ref.		62	18.0	46	18.0	--
	Ref.		35	8.5	+ 1	14.9	--
	Ref.		22	9.8	-12	14.5	48
K. T.	B.		57	6.2	52	17.7	60
	B.		63	4.7	53	13.7	--
	Ph. Cr.		55	3.8	52	11.7	--
	Ref.		35	15.2	22	19.6	42

Angles of the average vectors with the horizontal and manifest values (*man. val.*) in μv seconds* at various stages of the treatment, viz.: *B*, before treatment; *Ph. Cr.*, phrenic crush; *P. P.*, induction of pneumoperitoneum; *Ref.*, refill; *P.a.*, pneumoperitoneum abandoned.

*Due to a fault in the instrument all the recorded voltages were low. Comparison with Ashman and Byer indicates that our voltages should be about twice those recorded. This does not affect the conclusions which are based on the relative values in the different leads.

vertical line between that point and the base line separates the S deflection from the T wave for our purposes. This arbitrary choice does not, of course, influence the values and directions of the gradient vector. That the choice was justified is demonstrated by the fulfilment of the Einthoven triangle condition for the QRS vector as shown in Table VI.

Table VI gives the manifest values and directions of the two vectors at the various stages of the pneumoperitoneum treatment. These stages are indicated by the following abbreviations: *B*, before treatment; *Ph. Cr.*, phrenic crush; *P.P.*, the induction of the pneumoperitoneum; *Ref.*, a refill; and *P.a.*, that the treatment has been abandoned, although it does not necessarily mean that the diaphragm has returned to its initial position, as phrenic paralysis may persist. The geometric position of the heart, as obtained from anteroposterior roentgenograms, is given in the last column. The procedure followed in the measurements was that described by Roesler,[6] though it is to be borne in mind that the determination of the movement of the longitudinal axis on a roentgen film is met with great difficulties, since after the diaphragmatic rise the heart shadow can attain an entirely different shape, and sometimes the position of the apex cannot be assessed with certainty. However, a

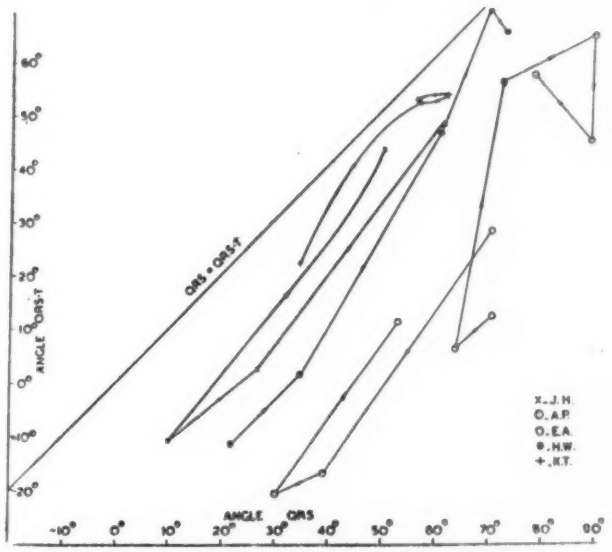


Fig. 7.—The QRS-T angles plotted against those for QRS, from Table VI. Lines with arrow heads indicate the points belonging to the same case. The points follow a well-defined trend; as the diaphragm rises the separation between QRS and QRS-T increases.

rough idea can be obtained, and from the figures shown in Table VI it is evident that the electrical vectors carry out much greater movements than are shown by the radiographic measurements. The marked rotation towards the left, as indicated by the electrical vectors, must be described as a pronounced left axis deviation. For example in the case of J. H., the QRS vector is deviated toward the left by 52 degrees and the gradient vector, by 59 degrees. In most instances the angular separation of the two vectors increases as the diaphragm rises. The angular positions of the vectors with regard to the horizontal axis in the course of P.P. are demonstrated in Fig. 7, in which, following the example of Ashman and Byer,[4] the angle of the QRS-T complex is plotted against that of QRS complex for the cases in Table VI. It is clear that the position of the heart changes in a very well-defined manner.

Adopting the findings of Ashman, Gardberg, and Byer[7] it is possible to describe the change of position of the heart in simple terms. These authors have shown that in the normal heart the gradient vector lies behind the longitudinal axis of the heart; the axis points slightly forward and to the left. The QRS vector lies back still further. The two vectors and the longitudinal axis of the heart lie nearly in one plane; the angle between the axis and the gradient

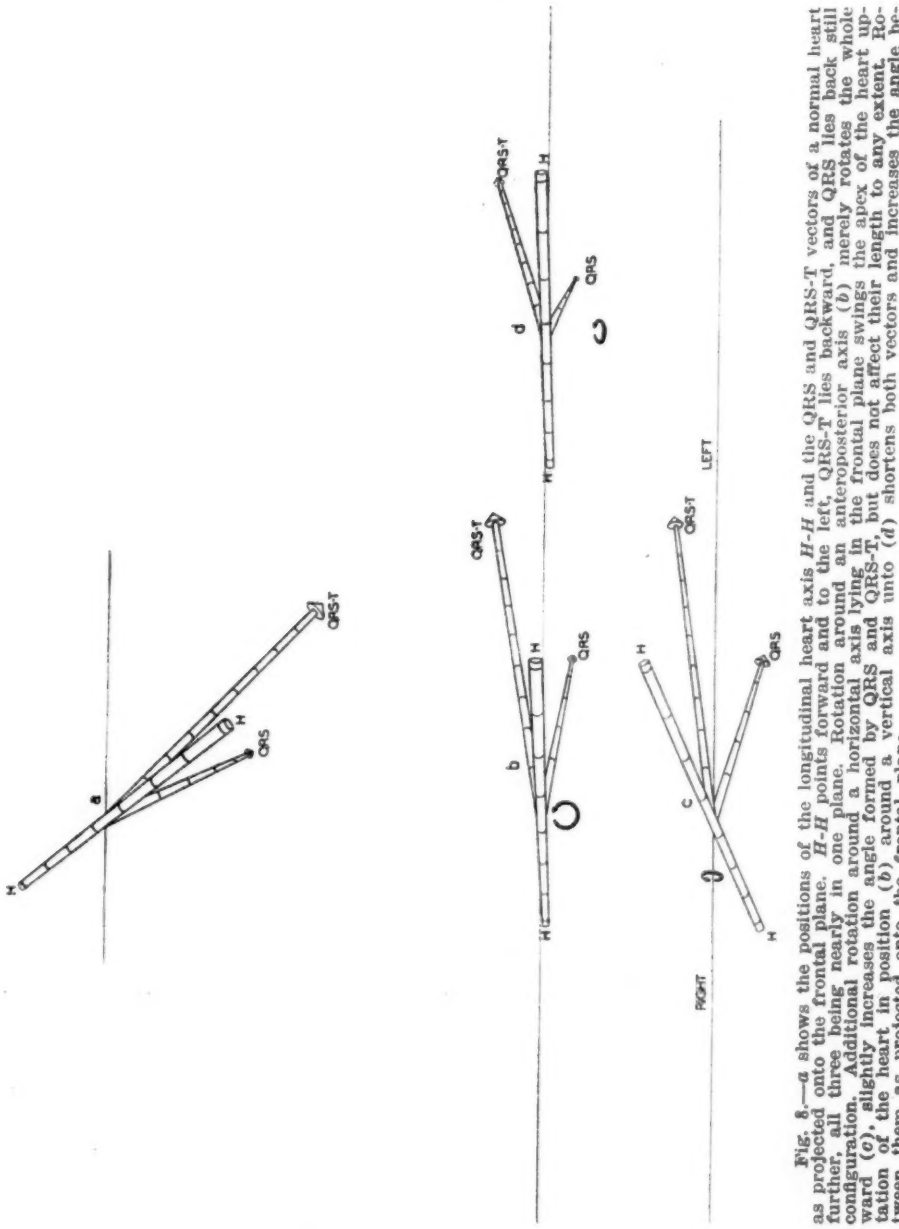


Fig. 8.—*a* shows the positions of the longitudinal heart axis *H-H* and the QRS and QRS-T vectors of a normal heart as projected onto the frontal plane. *H-H* points forward and to the left, QRS-T lies backward, and QRS lies back still further, all three being nearly in one plane. Rotation around an anteroposterior axis (*b*) merely rotates the whole configuration. Additional rotation around a horizontal axis lying in the frontal plane swings the apex of the heart upward (*c*), slightly increases the angle formed by QRS and QRS-T, but does not affect their length to any extent. Rotation of the heart in position (*b*) around a vertical axis unto (*d*) shortens both vectors and increases the angle between them as projected onto the frontal plane.

is approximately 60 degrees, and that between the axis and the QRS vector is approximately 90 degrees. The length of the gradient vector in space (as against its projection onto the frontal plane) is about twice that of the QRS vector. This situation is depicted for a heart in a fairly normal position in Fig. 8, *a*, where the length of each vector corresponds to the projection onto the frontal plane given in Table VI (J. H.). The rise of the diaphragm transfers

the vectors into positions indicated in Fig. 8, *b*, *c*, and *d*. What this movement means in terms of movement of the heart itself is best demonstrated by means of a solid model of the heart and its attached vectors, a shadow image of which is thrown onto a piece of paper representing the frontal plane. In this way it is seen that the movement of the vectors and thus of the heart consists in the main of a rotation about an anteroposterior axis. This rotation is anticlockwise if we look at the front of the body and transfers the longitudinal axis of the heart *H-H* and the vectors into the position *b*. We have seen, however, that the angle between the QRS and the QRS-T vectors increases on raising the diaphragm. This increase may be brought about in two ways: either by a rotation about a transverse axis which would leave the lengths of the vectors as measured in the frontal plane essentially unaffected (this is indicated in Fig. 8, *c*) or by a rotation around a vertical axis affecting very strongly the lengths of the projected vectors (Fig. 8, *d*). Most of the cases analyzed show rotation about the transverse axis, but the case of J. H. appears to represent a rotation about a vertical axis.

The number of cases analyzed does not allow any more general conclusions regarding the movement of the heart produced by pneumoperitoneum. It is clear that the present analysis has not exhausted the possibilities offered by this and similar operations to the study of the heart activity and in particular of the fundamental average vectors. At present the results of previous work had to be used in order to derive the movement of the heart from the electrocardiogram; the correctness of our interpretation depends entirely on these results which were derived and generalized from a study of a large number of normal human hearts in different positions of the body. The possibility of displacing the same heart, largely at will, offers the attractive prospect of determining directly the geometric relationship of the various vectors and the heart and the body.

SUMMARY AND CONCLUSION

1. The treatment of pulmonary tuberculosis with pneumoperitoneum offers the opportunity of studying the cardiovascular changes in the presence of a markedly raised diaphragm.

2. No cardiovascular distress has been observed with this kind of treatment, even if one diaphragm rises as high as the second rib anteriorly.

3. The vital capacity was measured in a number of patients; after months of treatment with pneumoperitoneum refills of 1,000 to 1,400 c.c. of air, some of them showed no change at all, others showed a slight increase, and some showed a decrease.

4. The normal electrocardiogram develops the Q_3T_3 pattern and the S-T deflection in Lead II becomes flattened. No signs of coronary thrombosis or pulmonary embolism have been noted. The pattern is reversible and becomes normal again with the descent of the diaphragm.

5. A study of the QRS vector and of the ventricular gradient demonstrates that the change of the electrocardiographic pattern is due in the main to a rotation of the heart around an essentially horizontal axis lying in the sagittal plane, the rotation to be described as anticlockwise, as one looks from front to back, i.e., the apex moves upward toward the left.

6. This accounts for the often striking distortion of the heart silhouette in the roentgenogram. The apex sometimes becomes buried in the heart shadow. Measurements of the displacement of the heart on the roentgenogram are therefore not reliable.

7. The conclusion to be drawn from the clinical observations together with the results of investigations of vital capacity and electrocardiogram is that pneumoperitoneum treatment in a tuberculous patient with a normal heart does not entail any danger from the cardiovascular point of view.

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THE RELATION OF AGE AND OTHER FACTORS TO CARDIAC SUBENDOTHELIAL HEMORRHAGE IN DOGS

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THE observation that large and small hemorrhages into the heart valves of dogs occurred with surprising frequency in examinations of animals employed for physiologic investigation prompted this study. The occurrence of cardiac subendothelial hemorrhage, spontaneously or as a result of experimental procedures, is of interest for several reasons: first because the lesions in the blood vessels responsible for such hemorrhages may be a measure of similar lesions elsewhere, which may be more difficult to observe; second, because the occurrence of such lesions may have a bearing on the age incidence of vascular disease; and third, because conditions which cause subendothelial valve hemorrhages may play a role in the etiology of such diseases as rheumatic and bacterial endocarditis. The observations reported here may provide a basis for an experimental approach to practical problems in these fields.

MATERIALS AND METHODS

Mongrel dogs of various ages were employed in this study. One hundred seventy-eight animals were used. The observations fall into three groups:

1. Observations were carried out on the hearts of eighty-six dogs of various ages, mostly killed in the laboratory for other experiments. Nineteen animals,

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anesthetized with ether, were bleeders for heart-lung preparations. Nineteen were used for cerebral cortex stimulation; these, also, were anesthetized with ether. Eleven animals were killed by intravenous infusion of lanatoside C without anesthesia. Ten were anesthetized with ether and employed in respiration studies. Nine were anesthetized with nembutal for two hours and employed in intestinal absorption experiments. Eight were killed with overdoses of nembutal or ether. Eight were killed by intravenous injection of potassium cyanide solution without anesthesia. In no instance was a pressor drug employed. There were no apparent differences in the observations in the several groups, and they will be treated as one. In these animals a careful autopsy examination of the interior of the heart was made and tissues were removed for microscopic examination after fixation in Zenker-formalin solution and hematoxylin and eosin staining.

2. Forty-four dogs were studied specifically with respect to the incidence of valve hemorrhages in relation to the effects of epinephrine and pitressin.

3. Forty-eight dogs were studied specifically with relation to a possible antagonism between papaverine, vitamins P or C and epinephrine or pitressin in connection with the hemorrhagic tendency.

All animals in Groups 2 and 3 were killed by intravenous injection of 10 per cent potassium cyanide solution without anesthetization.

The presumed ages of the animals were ordinarily obtained from the dealer, who was requested to obtain as accurate information as possible from the original owners. The dogs were bought from farmers by this dealer. In a number of instances, where no such information could be obtained, the age was estimated from the condition of the teeth by an experienced animal caretaker and recorded before any other observations were made. In these estimates of age, emphasis can be placed only on the results with young and old animals.

In Series 2 and 3 the animals were treated with various agents, as indicated in each case. The sex was noted in each case, but they are not separated in the results because there was no striking sex difference in the findings.

RESULTS

1. *The Factor of Age.*—The occurrence of subendothelial hemorrhages, particularly into the mitral valve leaflets, but less often into the aortic and tricuspid valve leaflets was noted. Fig. 1 shows a typical example of a mitral valve with a punctate and larger hemorrhagic areas. Fig. 2 shows a low-power microscopic section of such a hemorrhagic valve. Fig. 3 is a high-power view of a portion of the same valve showing massive subendothelial hemorrhage. Table I shows the incidence of subendothelial hemorrhages in the valves of the hearts of dogs in relation to age. It will be seen that three and one-half times as many old dogs showed cardiac valve hemorrhage in this series of observations as did young mature animals. It is believed that no factor other than age entered into this difference because no known selective factor entered into the choice of animals for study.

2. *Hemorrhage Induced by Vasospastic Agents.*—Since the younger animals showed fewer spontaneous valve hemorrhages, the influence of various agents up-

TABLE I. SUBENDOTHELIAL HEART VALVE HEMORRHAGE IN DOGS IN RELATION TO AGE

AGE RANGE (YR.)	NUMBER OF ANIMALS	NUMBER WITH HEMORRHAGE	PERCENTAGE WITH HEMORRHAGE
1 to 3	31	6	19
3 to 5	36	17	47
5 and over	19	13	68

TABLE II. THE INFLUENCE OF ISOTONIC SALINE, EPINEPHRINE, AND PITRESSIN UPON HEART VALVE HEMORRHAGE IN DOGS

NUMBER OF ANIMALS	AGE RANGE (MONTHS)	DRUG TREATMENT	KILLED AFTER (DAYS)	NUMBER WITH HEMORRHAGE	PERCENTAGE WITH HEMORRHAGE
4	6 to 8	Saline*	1	0	0
4	5 to 6	Saline*	14	0	0
4	4 to 8	Epinephrine†	1	3	75
4	6 to 7	Epinephrine†	14	1	25
4	4 to 8	Pitressin‡	1	4	100
4	5 to 6	Pitressin‡	14	1	25
2	24 to 48	Saline*	0	2	100
10	18 to 48	Epinephrine†	1	8	80
2	24 to 48	Pitressin‡	0	2	100

*The intravenous injection of 0.5 c.c. of saline four times at two-hour intervals served as a control on the other experiments.

†Dose: 0.5 c.c. of 0.1 per cent epinephrine four times at two-hour intervals.

‡Dose: 0.5 c.c. of pitressin (Parke, Davis and Company) four times at two-hour intervals.

Fig. 1.—Gross appearance of the mitral valve of a dog showing hemorrhagic lesions at the points indicated by arrows.

on such lesions was studied first in dogs known to be less than 1 year old. Observations were made upon the effects of intravenous injections of 0.5 c.c. of 0.1 per cent adrenalin, repeated four times at two-hour intervals, with death of the animal either immediately, twenty-four hours, or two weeks later by intravenous potassium cyanide. Similar experiments were performed using the afore-mentioned doses of Pitressin (Parke, Davis Company). These experiments were controlled by giving equal quantities of isotonic saline to comparable numbers of animals of the same ages. The results appear in Table II in which it is evident that, when 5- to 8-month-old dogs are killed by potassium cyanide, after a control injection of saline, no subendothelial hemorrhages are seen. In the case of the 2- to 4-year-old dogs given saline, both showed hemorrhages. These observations are in confirmation of the results shown in Table I. The ten animals in the saline control series here were not included in Table I. If they are so added, the age difference shown in that table would be even more pronounced.

However, when either epinephrine or pitressin was given to young dogs killed within a day thereafter, hemorrhages appeared in 75 and 100 per cent of the animals, respectively. When death was delayed until two weeks after drug injection, hemorrhage was still evident in one dog out of four. With older

animals the incidence of hemorrhage with either drug was nearly 100 per cent, as might be expected. The important result is that after the employment of adrenalin and pitressin subendothelial hemorrhages were seen in young dogs which otherwise did not present such lesions.

Fig. 2.—Low-power view of a section of a mitral valve leaflet of a dog showing a large hemorrhagic area. Zenker-formalin fixation and hematoxylin-eosin staining (magnified ×30).

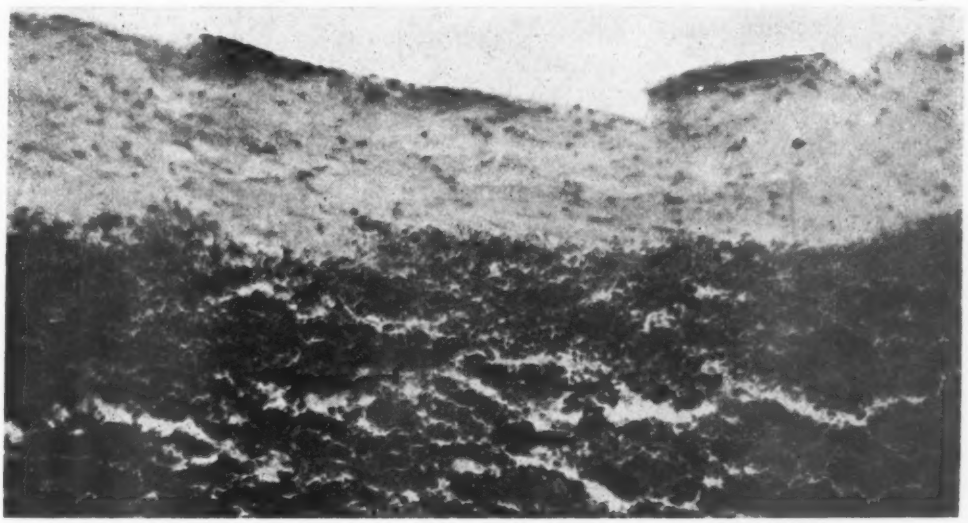

Fig. 3.—High-power view of a portion of the valve shown in Fig. 2 (magnified ×240).

3. *Unsuccessful Attempts to Counteract the Hemorrhagic Effects of Epinephrine and Pitressin.*—Since ascorbic acid and vitamin P (citrin) have been shown to have an effect in preventing certain types of hemorrhage[1-3] it was thought desirable to test their effects upon the hemorrhagic effects of the two agents employed in these studies. Three series of experiments were performed. In the first, 500 mg. of ascorbic acid were administered daily for seven days, by capsule, before the vasospastic drug was given. In the second, the same doses of citrin were given. In the third, 150 to 200 c.c. of whole lemon water extract were given daily for fourteen to twenty-eight days by stomach tube. The lemon extract was prepared by placing forty-eight finely sliced lemons in a liter of water, boiling for ten minutes, macerating, cooling, filtering twice through gauze, and preserving on ice. This water extract contains both ascorbic acid and citrin besides other substances.

The results of these experiments are shown in Table III. Neither ascorbic acid nor citrin, in the doses used, exhibited any protective effect against

TABLE III. OBSERVATIONS ON ASCORBIC ACID AND CITRIN IN RELATION TO HEART VALVE HEMORRHAGE IN DOGS

NUMBER OF ANIMALS	AGE RANGE (MONTHS)	PRE-TREATMENT			DRUG TREATMENT	NUMBER WITH HEMORRHAGE	PERCENTAGE WITH HEMORRHAGE
		DRUG	DOSE PER DAY (MG.)	TIME (DAYS)			
2	2 to 3	Ascorbic acid	500	14	Saline*	0	0
2	2 to 3	Ascorbic acid	500	14	Epinephrine†	2	100
2	2 to 3	Ascorbic acid	500	14	Pitressin‡	2	100
2	3	Citrin	500	14	Saline*	0	0
2	3	Citrin	500	14	Epinephrine†	2	100
2	3	Citrin	500	14	Pitressin‡	1	50
4	8	Lemon extract	175	14	Epinephrine†	3	75
4	5 to 10	Lemon extract	175	21	Epinephrine†	3	75
4	6	Lemon extract	175	28	Epinephrine†	4	100
6	10	Lemon extract	175	18	Pitressin‡	5	83

*Dose: 0.5 c.c. four times at two-hour intervals one day before death with potassium cyanide.
†Dose: 0.5 c.c. of 0.1 per cent epinephrine four times at two-hour intervals one day before death with potassium cyanide.
‡Dose: 0.5 c.c. four times at two-hour intervals one day before death with potassium cyanide.

adrenaline, and an effect on the pitressin action is improbable, especially because nothing significant was seen with six dogs given lemon extract for eighteen days. It is concluded that ascorbic acid and citrin do not have a protective effect against adrenaline and pitressin when given in massive doses over a two- to four-week period.

In addition to the experiments outlined, studies were made on six dogs, 2 to 10 months of age, in which 10 to 20 mg. of papaverine per kilogram of body weight were administered subcutaneously from twenty to ninety minutes before each injection of epinephrine or pitressin in the usual doses. Of these six animals, five showed the characteristic hemorrhages. Thus, papaverine, which is an effective coronary dilator,[4] did not, in the manner used, prevent the hemorrhagic effects of epinephrine and pitressin.

DISCUSSION

Nedzel[5, 6] employed pitressin in studies on the production of bacterial endocarditis in dogs. He reported finding endothelial swelling following pitressin administration but did not mention the occurrence of subendothelial hemorrhage. He inferred that pitressin facilitated the production of experimental endocarditis. Dearing[7] and Dearing et al.[8] noted a high incidence of localized myocardial degeneration in cats treated with large doses of pitressin. They noted "small macroscopic reddish verrucae . . . in the mitral valves in some of the animals. Subendocardial hemorrhages were observed macroscopically in several animals. . . . The old animals (5 cats) were the only ones which developed myocardial lesions. Myocardial changes were not found in several young cats (4 animals)."

The lesions reported in this paper occurred with much smaller doses of pitressin than those reported by Dearing and his co-workers. He employed doses four to six times as great in cats as were used in this study in dogs. The relative sensitivity of the cat and dog to the actions in question may be different. No specific test of this question has been carried out. Nevertheless, it is interesting that young cats appeared to be more resistant to the hemorrhagic and myocardial degenerative effect of pitressin than are older animals.

The failure to prevent hemorrhages by ascorbic acid, citrin, and papaverine in these studies is not considered by the authors to have great significance. These agents were chosen for study because of their obvious relations, in the case of the first two, to small vessel hemorrhage, and in the case of the second, to

coronary constriction. In a systematic study of possible antagonists to this action of pitressin and epinephrine a much broader approach would be necessary. In fact it would be worth while, it is believed, to study the effects of the same agents under different conditions.

The experiments on attempted prevention of the hemorrhagic lesions are presented partly because they add to the proof that pitressin and epinephrine produce a high incidence of valve hemorrhage in young dogs. These observations can, without much doubt, be added legitimately to the data presented in Table II. If this is done one finds that, in sixteen dogs under 1 year of age given pitressin and killed within twenty-four hours, the incidence of valve lesions is 88 per cent. In the case of epinephrine the over-all incidence is also 88 per cent in twenty-four such dogs. This is in contrast to a zero incidence in twelve dogs under 1 year of age given control injections of saline. These figures are more impressive for statistical treatment than are those in Table II, alone. There can be no significant doubt about the reality of the pitressin and epinephrine effects in the light of the full data.

The frequent occurrence of valvular hemorrhage in routine autopsies on older animals requires discussion. It would be gratuitous to assume that the lesions seen after death were necessarily present before the animal was handled in any way. All animals were either anesthetized with ether or nembutal, or killed with intravenous potassium cyanide. In addition most of the anesthetized dogs were subjected to some experimental procedures, as indicated. None of the animals was specially "trained" for intravenous injection or other handling; therefore, it is likely that blood pressure elevation and vasomotor reactions occurred in most of the dogs during the several manipulations. It is still an open question whether death could be produced by any procedure which would not introduce some element of excitement, without an extensive training period. Furthermore, it would remain to be shown that any toxic substance employed as a lethal agent did not itself cause alterations in the blood vessels of the heart valves before it could be used to ascertain whether or not the valve hemorrhages existed before treatment.

Fortunately, the results here presented have some significance regardless of the precise mechanism of the development of lesions. The fact of the age difference in incidence is at once important because it demonstrates a defect in older animals as regards their ability to meet certain strains without damage. The fact that valve hemorrhages occur with such great frequency in older animals subjected to a variety of treatments suggests likewise that such lesions are likely to occur from time to time in the ordinary course of events in life. The excitement involved in anesthetization or intravenous injection of potassium cyanide under the careful conditions employed is probably not greater than that in many stress situations in life. Although we have no proof of the connection, it may be suggested that the roughened nodular valves seen with great frequency in autopsies of older humans, without rheumatic or bacterial endocarditis, could be the result of repeated hemorrhagic lesions of the type described here.

The greater frequency of occurrence of hemorrhagic lesions in older animals is also to be considered in connection with the age incidence of coronary vascular disease in the human. This is made more pertinent by the observations of Dearing on focal myocardial degeneration in cats. Both sets of observations point toward a greater susceptibility to damage under strain in older animals.

The present study obviously makes only a small beginning in the attack upon the problem. An exact physiologic analysis of the mechanism of produc-

tion of subendothelial hemorrhage is essential to further progress. It must be ascertained whether (1) blood pressure elevation, (2) extreme local ischemia with resulting injury to vessel walls, or (3) other factors, are responsible for the lesion. It will also be necessary to account for the fact that the mitral valves are the sites of predilection for hemorrhage. It occurs to one that mechanical trauma may be greatest at this point. Further, it will be necessary to ascertain whether (1) alterations in the condition of the vessels or (2) differences in the response to strain, are the cause of the differences in reaction at various ages. Such an analysis could scarcely fail to yield information important to an understanding of the ageing process. This preliminary report is being made in order to call attention to what are believed to be important facts basic to the entire problem.

SUMMARY

1. Observations on the state of the endocardium, particularly of the heart valves, have been made in one hundred seventy-eight dogs in relation to age, injection of pitressin and epinephrine, and in connection with attempts to prevent the occurrence of lesions following the use of such agents.

2. The incidence of subendothelial heart valve hemorrhages in routine autopsies on laboratory experimental animals was found to be more than three times as great in dogs over 5 years of age as in animals under 3 years.

3. In twelve dogs under 1 year of age the incidence of valve hemorrhage was zero after control injections of isotonic saline and death by intravenous potassium cyanide solution.

4. In sixteen dogs under 1 year of age given pitressin and killed within twenty-four hours the incidence of valve hemorrhage was 88 per cent. The same incidence was seen in twenty-four such animals given epinephrine.

5. Neither ascorbic acid, vitamin P, nor papaverine counteracted the hemorrhagic effects of pitressin or epinephrine, under the conditions employed.

6. These observations may provide a basis for an experimental approach to clinical problems related to age and cardiovascular diseases.

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ANGINA PECTORIS WITH PARTICULAR REFERENCE TO ITS OCCURRENCE BEFORE AND AFTER MYOCARDIAL INFARCTION

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IT IS the purpose of this article to present the results of an analysis of a large number of cases of chest pain of the kinds that suggest to the patient or his medical adviser that the heart is the source of the difficulty. It is not necessary to review here the classical picture of angina pectoris or to discuss at length the prevailing views as to the mechanism which gives rise to the characteristic symptoms. It is generally admitted that this syndrome is due to disease of the coronary arteries or to an absolute, or relative, deficiency in the quantity or quality of the blood circulating through the coronary system and the Thebesian vessels. Heberden[1] noted that many patients complained of pains in the chest which proved to be annoying but not serious and sharply differentiated between these and the disorder under consideration, which he was the first to describe. In practice, however, the differentiation between anginal pain and other less serious kinds of pain is not always easy. For the purposes of analysis, we have divided our cases of chest pain into the following groups:

A. Poorly Characterized Pains.—In this group we have placed cases of momentary stabbing pain without radiation; of indefinite pain lasting for hours and not related to effort; and of pain which lasted for a few minutes, did not radiate, and was influenced by respiration. We have also included, in this group, patients seen in consultation because of rheumatic, pleural, or neuralgic pain and those in which the pain was apparently of psychic origin. There are two kinds of chest pain of cardiovascular origin which fall into this group because they do not present features which make it possible to identify them with any certainty. We refer to the pain of aortitis, sometimes not severe, and usually located behind the sternum, which often comes on after, though not during, severe exertion and to the pain of pericarditis which is usually accompanied by fever and may simulate the pain of myocardial infarction, but usually does not radiate and is not associated with a feeling of oppression. Finally, we have included in this group, certain cases of pain occurring in women, without hypertension or diabetes, which simulated the pain of myocardial infarction closely but in which there were no associated changes in the electrocardiogram and there was no feeling of illness on the day afterward. We have seen a number of very interesting cases of this kind.

B. Angina of Rest.—In this group, we have placed cases of paroxysmal pain beneath the sternum or in the precordium, which occurred at rest and was not precipitated by an obvious factor, was of short duration, was accompanied in most instances by a feeling of oppression, was relieved by nitroglycerin, and radiated to one or both arms, to the neck, or to the jaws. We have not included here cases in which there was a history of myocardial infarction or in which the electrocardiogram displayed changes characteristic of infarction.

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TABLE I

Total number of cases analyzed	2,248
Pains not well characterized	429
Angina of rest (cases without history of infarction)	35
Angina of effort (cases without history of infarction)	46
Infarction	208

TABLE II

Angina of rest	Absence of signs	2
	Arteriosclerosis of the aorta	6
	Syphilitic aortitis	5
	Arteriosclerosis of the aorta and hypertension	3
	Arteriosclerosis of the aorta and mitral insufficiency	1
	Hypertension	4
	Coronary sclerosis	5
	Aortic insufficiency	1
	Aortic insufficiency and mitral lesion	2
	Mitral stenosis	3
	Congenital heart disease (pulmonary stenosis)	1
	Paroxysmal tachycardia	1
	Hyperthyroidism	1
Angina of effort	Absence of signs	4
	Arteriosclerosis of the aorta	3
	Syphilitic arteriosclerosis of the aorta	4
	Syphilitic aortitis and hypertension	3
	Arteriosclerosis of the aorta and hypertension	3
	Hypertension	5
	Hypertension and coronary sclerosis	7
	Coronary sclerosis	9
	Aortic insufficiency	5
	Aortic insufficiency and mitral stenosis	2
	Mitral stenosis	1

C. Angina of Effort.—In this group, we have placed cases in which pain of the type described in the preceding paragraph was induced by effort, emotion, the taking of food, or by exposure to cold wind. Here, also, we have excluded cases in which there was a history of infarction or in which the electrocardiogram was characteristic of infarction, although there were some cases in this group in which the electrocardiogram showed some of the features described by Wolferth in cases of lateral infarction.[2]

D. Myocardial Infarction.—We have placed in this group cases of anginal pain that was prolonged in the vast majority of cases and was accompanied by electrocardiographic changes that were characteristic of infarction from the first, or underwent the characteristic evolution.

The total number of case histories analyzed was 2,248; we placed 429 of these in the first group, 35 in the second, 46 in the third, and 208 in the fourth. The classification of the cases of angina of rest and angina of effort according to the type of heart disease present is shown in Table I. It will be noted that, of the 289 cases of anginal pain, there were 208 in which the pain was associated with infarction. The history of these cases of infarction showed that in most instances the patient experienced angina of rest or angina of effort, either before, or after, the coronary accident (Table II). Some patients had angina of effort and angina of rest simultaneously either before, or after, infarction occurred (Table III).

We found, then, a very high incidence of angina pectoris before or after infarction. Had our study been more complete, the incidence might have been still higher. Many of our observations on cases of infarction were relatively recent, and it was not possible to determine whether anginal pain would occur

TABLE III

Total number of cases of infarction	208
With angina of rest preceding the attack	66
With angina of effort preceding the attack	46
With angina of rest succeeding the attack	41
With angina of effort succeeding the attack	57

TABLE IV

Total number cases of infarction	208
With anginal manifestations pre or post infarction	137
Without anginal manifestations pre or post infarction	71

when the patient returned to a more or less normal life. It is also probable that infarction had occurred in some of the cases classified as angina of effort but could not be diagnosed because the electrocardiographic changes due to infarction had disappeared and the history did not give the necessary information. It will be noted that angina of rest preceded infarction frequently. It is possible that its frequency after infarction is less than our tables indicate. In some instances, the attacks of pain considered angina of rest may have been induced by some factor that was not noted. There were also some cases classified as angina of rest in which the patient had a series of attacks of pain separated by short intervals; these may have represented the gradual development of an infarct or a series of minor coronary accidents. Judging by those cases, which were under observation for a long period, angina of rest after recovery from infarction is infrequent.

Angina of effort after infarction is much more common. This type of angina occurs under other circumstances (in syphilitic aortitis, in mitral or aortic stenosis, in hypertension, in anemia, and in hyperthyroidism) when there is a deficient flow of blood through the coronary arteries during strenuous exertion. But the incidence of angina of effort in these conditions is small in relation to the number of cases in which it precedes or follows myocardial infarction, and the disparity would be greater if more information concerning the subsequent history of patients seen in consultation were available and more extensive electrocardiographic studies had been carried out during periods following the more severe and prolonged attacks of pain.

We are aware that our views concerning the relation of angina pectoris to infarction are not in accord with those held in many medical centers. We may point out that, if syphilitic aortitis were a common cause of angina pectoris, one would expect to encounter in Brazil, where syphilis is a very common disease, many cases of anginal pain due to syphilitic narrowing of the coronary orifices. In our experience, however, cases of this kind are rare in comparison to the number of cases of anginal pain before or after infarction.

Our observations on the close relation between infarction and angina pectoris have led us to investigate cases of this disorder with considerable care. The prognosis and the treatment must be based, first of all, upon a detailed and carefully taken history. When the history is taken by one who is very familiar with the symptomatology and conscious of the importance of details, it provides information that cannot be obtained in any other way.

Usually, angina of rest and angina of effort can be easily differentiated. The former is spontaneous and paroxysmal, but it is not always intense. The discomfort is usually located beneath the sternum, in the precordium, or in the epigastrium, and often radiates to the arm. It is sometimes felt in the shoulders,

elbow, or wrist, and, when this is the case, it is not influenced by movement of the joints of the extremity affected. Angina of rest is very frequently followed by infarction, and this is probably why it has been considered one of the most serious of cardiac symptoms. Whenever a diagnosis of angina of rest is made, and whenever the history suggests that it may be present, we advise the patient to be extremely careful. We often take this precaution in cases where there has been rather indefinite pain, or painful discomfort, of brief duration beneath the sternum, in the precordium, or in the shoulders or arms. It is clear that there is a great possibility of error in diagnosis in such cases, but to learn that a patient who has been told that his discomfort is of no consequence and has been reassured has died soon afterward from a coronary occlusion is a very disagreeable experience which we, like most physicians, wish to avoid.

Some patients with typical angina of rest, before or after the occurrence of infarction, have rather prolonged crises at frequent intervals, as if there were a succession of minor infarctions. In some of these cases, the form of the electrocardiogram varies from one attack to another. The occurrence of sudden death after a series of such anginal attacks or the development of characteristic electrocardiographic changes strongly suggests that a series of small infarctions ended in a major one.

In angina of effort, the diagnosis is easier, but it should be remembered that the location of the pain is quite variable; it may be in the wrist, elbow, neck, epigastrium, or right upper quadrant of the abdomen, rather than beneath the sternum. We believe that pain in the thorax or upper abdomen, which is clearly precipitated by effort, is due to coronary insufficiency in all except very rare cases. Angina of effort which precedes infarction often displays a rapid increase in severity which enables us to foresee the outcome: the patient complains that he has been having the pain for weeks or months, but that every day he feels worse and develops pain after less exertion. There are, however, curious cases in which the effect of effort is very variable.

In the case of syphilitic aortitis with narrowing of the coronary orifices, and in aortic insufficiency, angina of effort usually evolves slowly, often over a period of years.

Angina of effort after infarction is more frequent than angina of effort before infarction. We believe that the former would be still more common if it were not customary to keep the patient at rest for a long period following the coronary accident. It is logical to suppose that a seriously injured heart will not tolerate the strain imposed by effort without producing unfavorable reactions. There are, however, occasional cases of recent infarction in which exertion does not produce pain. The occurrence of cardiac pain, like the occurrence of pain of other types, is determined to some extent by psychic factors; this probably explains why, after a coronary accident, some patients complain of pain which is sometimes vague and at other times more intense and does not seem to be closely related to the work imposed upon the heart. In such cases, it is often difficult to know whether the pain should be attributed directly to the infarction, to disturbances in coronary circulation due to emotional reactions, or to purely psychic causes.

Arthritic symptoms are not uncommon after infarction and sometimes develop several months after a coronary accident. The shoulder is the joint most often involved and the pain is closely related to movement of the arm, which clearly indicates that it is not anginal.[3]

When angina of effort does not appear during convalescence from myocardial infarction, under circumstances which commonly induce it, and dyspnea is also absent, the prognosis is naturally favorable. The prognosis is also favorable when, as often happens, angina of effort does occur in the earlier stages of convalescence but becomes less frequent and requires more effort to induce it as time goes on and, eventually, disappears. This is particularly true when no enlargement of the heart takes place.

It is interesting that angina of rest of short duration is rare after infarction. In contrast to the situation that obtains before infarction, we can almost always ascertain what the provoking factors are when anginal pain occurs after infarction: physical effort, emotion, reflexes, or other effects associated with digestion.

SUMMARY

Angina of rest and angina of effort may occur under a great variety of circumstances, but in the vast majority of cases they precede or follow myocardial infarction. In syphilitic aortitis and diseases other than those which lead to myocardial anorexia by direct involvement of the coronary arteries, angina pectoris is, by comparison, infrequent.

Angina pectoris is usually more severe when it precedes, than when it follows, infarction; and angina of rest is very much more common before, than after, infarction has occurred, particularly if we exclude from this category the pains separated by short intervals that sometimes accompany the crisis. When anginal pain following infarction is not related to exertion, it is often due to other precipitating factors and the diagnosis of angina of rest, if this is defined as spontaneous anginal pain, is difficult.

Angina of effort, which displays a rapid increase in severity and requires less and less effort to induce it, suggests that infarction is imminent. After infarction, the absence of angina of effort or a progressive decrease in its severity is a favorable omen. In such cases, we believe that a gradual increase in the patient's physical activity is beneficial.

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FACTS AND FALLACIES ABOUT THE NORMAL APEX BEAT

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PALPATION of the precordium in health and disease is a valuable diagnostic procedure. The location of the apex beat gives first rate evidence regarding the size of the heart. It furnishes evidence of the size of the heart as valuable as that shown by fluoroscopy. When demonstrable, it is a more valuable sign of the heart size than roentgenograms, as usually taken, in full inspiration.

On reviewing the information regarding the apex beat presented in the textbooks of physical diagnosis and cardiology, one is struck by the uncritical discussions of this subject. This is evident in the following excerpts: Paul D. White[1] in regard to locating the apex beats, states, "This is possible in the majority of cases, failing only in a few obese or very sick patients." Norris and Landis[2] in discussing the cardiac impulse, observed that the intensity depends on "(a) rapidity and the force of the ventricular contraction, (b) the shape of the chest, (c) the amount and the character of the overlying soft tissue . . . in deep chested or corpulent individuals . . . may be imperceptible." (Sutton[3] states: "Apex beat is the forceful projection of the apex against the chest wall." "Force varies widely in different individuals." "When the apex beat cannot be felt, leaning the body forward may make it more readily palpable." Pratt and Bushnell[4] state: "Up to the twentieth year the cardiac impulse can be felt in practically every chest in health. With increasing age it can be less readily palpated, and by age fifty it can be felt in about forty per cent of the people. In old age it becomes again more frequently palpable." Cabot and Adams[5] state that the apex impulse is visible in most persons. "More accurate localization of the maximum impulse, than is possible by inspection, can often be made by palpation." Alfred L. Loomis[6] writes: "The cardiac impulse is visible in the majority of persons." "Palpation determines the force of the cardiac pulsation." Sahli[7] states, "An impulse synchronous with the heart action . . . can be felt over the precordia of healthy individuals." Majors,[8] in discussing points of maximum impulse, says, "This is normally located in about the fifth costal interspace inside the mamillary line." He also quotes William Harvey in *De Motu Cordis,* "The heart is lifted and rises up to the apex, so that it strikes the chest wall at that moment and the beat may be felt on the outside." Sterns[9] says, "The apex can generally be located (by palpation)."

Elias states,[10] "Apex Beat" . . . "Normally palpable in the 4th or 5th interspace, but may not be." Selective Service Regulations[11] require "Location and determination of the character of the apex impulse." Elmer and Rose[12] write, "In normal subjects the point of maximum intensity of impulse is seen in the fifth intercostal space just inside the midclavicular line." Anderson[13] writes, "Though usually found in the left fifth intercostal space within the nipple line, it is subject to change even in a normal chest." Hope[14] says, "The apex beats between the cartilages of the fifth and the sixth left ribs at a point about two inches below the nipple, and one inch on its sternal side."

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From these quotations it is apparent that the subject is treated in generalities. The impression is invariably left that the apex is normally always present, having features identifying it as easily as the "nose on the face." Dressler[15] seems to be the only exception to this point of view. In his presentation on pulsations of the chest wall he discusses the subject as follows:

"The apex beat is the most prominent pulsatory phenomenon caused by the contraction of the normal heart. This is a circumscribed systolic elevation, one to two centimeters in width, felt at, or somewhat inside of the midclavicular line in the fifth interspace in adults. The apex beat is usually well developed in children, becoming less distinct between ages of twenty to thirty years. In adults over thirty years a visible or palpable apex beat, noted in the recumbent position, should arouse suspicion that some pathological condition is present.

"The 'point of maximum intensity' may not always be synonymous with the 'apex beat,' as in various pathological conditions a powerful forward thrust is caused by segments of the heart quite distant from the apical area."

For many years it has seemed to us that the apex beat was absent more often than present. In doing insurance examinations, it seemed a bit compromising with the truth when it was necessary to describe the character and locate the apex beat in all individuals, usually spotting it accurately on an anatomic diagram (Fig. 1).

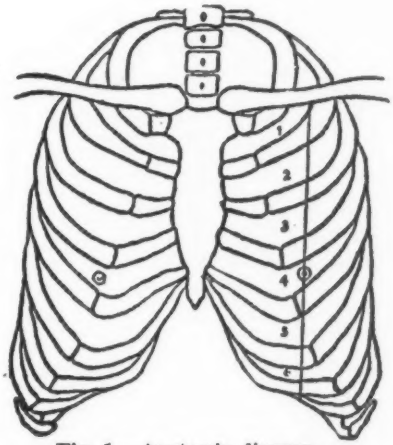

Fig. 1.—Anatomic diagram.

METHOD

It was apparent that all apex beats were not equally visible or palpable, so a simple system of grading was conceived:

Apex Beat (point of maximum intensity in normal hearts).—Grades (indicating its absence or its degree of presence):

0. Complete absence of any suggestion of a pulsation, at or near, the apical region.
1. Some pulsation, but indefinite; cannot be used as an indication of the location of the apex beat or the size of the heart.
2. Apex can be located; it may be faint, but it is definite. It may be only visible, or palpable, or both. It may be present only in the erect, prone, or leaning forward position, or in all positions.
3. Apex beat definitely palpable and usually visible. Typical "nose on the face" type.

Cardiac Impulse.—

This refers to any pulsation caused by the heart in the precordium with, or without, an apex beat.

The relation of the heart to the exterior surface of the precordium has been referred to, by the term, "heart accessibility." Factors influencing this situation are (1) the thickness of the chest wall, due to bones, muscle, and fat (in women the mammary gland), (2) the contour of the chest, least favorable in the barrel type, and (3) lung distention, fully developed in emphysema. These factors are not sufficiently emphasized in teaching students or appreciated by practitioners.

In order to obtain some definite information, it was decided to record the results of palpation of normal hearts. All cases of cardiac disease were excluded. These findings were recorded as a part of regular physical examinations. The precordium was inspected in good light. In women the breasts were lifted. Both inspection and palpation were done in the erect and the recumbent position and, if negative, in the leaning forward position. Time consuming procedures were purposely avoided. It was estimated that not more than thirty seconds were added to the time for examination. The apex beat was graded and recorded according to the previous classification. The cardiac impulse was recorded as to whether it was absent or present, but the intensity of the impulse was not graded.

The precordia of 1,000 persons with apparently normal hearts were inspected and palpated. The results were recorded, as indicated previously. These were analyzed as follows: (1) How frequently can the apex be located definitely by inspection and palpation? (2) How frequently can the apex be located with sufficient accuracy to be used as an indication of the size of the heart? (3) What is the influence of age on the demonstrability of the apex beat? (4) How does body weight influence the demonstrability of the apex beat?

RESULTS

It became apparent, early in this study, that little was gained by grading the intensity of the apex beat beyond definitely establishing its absence or presence. However, grading into four degrees was continued during the whole study. It did stimulate greater scrutiny and, for this reason, should be continued for a system of grading.

The important facts regarding the absence or presence of the apex beat can be better studied by combining Grade 0 and Grade 1 as the nonapparent type, since neither of these grades locate the apex beat or furnish any evidence of the size of the heart, and combining Grades 2 and 3 as the apparent type, both of which give first class evidence of the size of the heart.

Fig. 2 shows the incidence of combined apparent and nonapparent apex beats in males and females according to age. It is strikingly evident that, after 20 years of age, the apex beat becomes less demonstrable. This is less evident in women than in men but occurs in both sexes. Up to 20 years of age, the apex can be distinctly felt in 54 per cent of males and 55 per cent of females; between 20 and 30 years of age it drops to 27 per cent of males and 39 per cent of females. This progressive decline is graphically shown in the chart.

Fig. 3 shows the incidence of the apparent and nonapparent apex beats as influenced by the body weight. Weight is a very important factor in the accessibility of the heart and in the demonstrability of the apex beat. Again, the apex beat is more frequently demonstrable in females. In the weight range from 100 to 120 pounds the apex beat is a distinct sign in 45 per cent of males and 46.8 per cent of females. With increase of the body weight the demonstrability of the apex beat rapidly decreases, somewhat faster in the males than in the females.

The overall demonstrability of the apex beat is shown in Table I according to age, showing a definite apex beat absent in 76 per cent (Grade 0, 56 per cent; Grade 1, 20 per cent) and present in 24 per cent (Grade 2, 10 per cent; Grade 3, 14 per cent) of normal individuals.

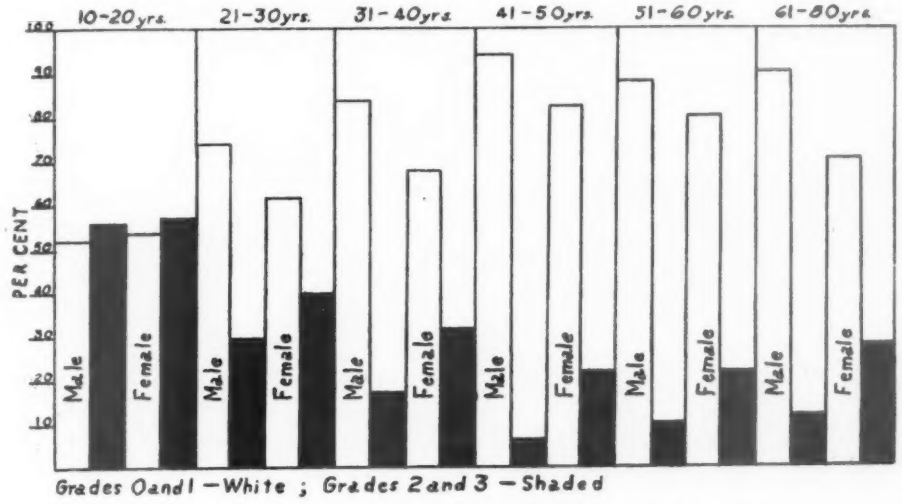

Fig. 2.—Apparentness of the apex beat according to age and sex.

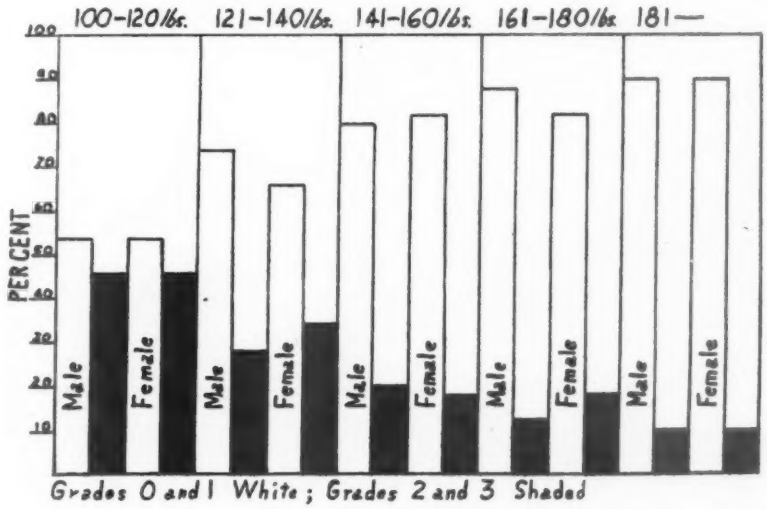

Fig. 3.—Apparentness of the apex beat according to body weight and sex.

Table II shows the same relation according to weight. In 74.8 per cent (Grade 0, 54 per cent; Grade 1, 20.8 per cent) of subjects the apex beat was absent. In 25.1 per cent (Grade 2, 10.8 per cent; Grade 3, 14.3 per cent) it was demonstrable.

Tables III and IV show the actual numbers of individuals studied and the percentage in each group according to age. Tables V and VI show the same relation for individuals according to weight.

CONCLUSIONS

1. Critical inspection and palpation of the precordia of 1,000 normal persons reveal the fallacies in the teachings regarding the normal apex beat.

TABLE I. ALL AGES

SEX	APEX BEAT 0		1		2		3		CARDIAC IMPULSE ABSENT		PRESENT	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Male	336	67.7	77	16	33	6.5	49	9.8	414	83.6	81	16.4
Female	224	44.3	123	24.3	67	13.3	91	18	357	70.5	148	28.5
Total	560	56	200	20	100	10	140	14	771	77	229	23

TABLE II. ALL WEIGHTS

SEX	APEX BEAT 0		1		2		3		CARDIAC IMPULSE ABSENT		PRESENT	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Male	332	67	79	16	32	6.5	52	10.5	404	81.6	91	18.4
Female	209	41.4	129	25.6	76	15	91	18	353	70	152	30
Total	541	54	208	20.8	108	10.8	143	14.3	757	75.7	243	24.3

TABLE III. AGE GROUP OF MALES

AGE (YRS.)	APEX BEAT 0		1		2		3		CARDIAC IMPULSE ABSENT		PRESENT	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
10-20	14	28	9	18	9	18	18	36	24	48	26	52
21-30	29	45.9	17	72.1	7	11	10	16	47	74.6	16	25.4
31-40	60	63.8	18	19.2	7	7.5	9	9.5	77	82	17	18
41-50	94	83.2	13	11.5	2	1.8	4	3.5	102	90	11	10
51-60	71	80	10	11	4	4.5	4	4.5	83	93	6	17
61-80	68	80	10	10.8	4	4.6	4	4.6	81	94	5	6

TABLE IV. AGE GROUP OF FEMALES

AGE (YRS.)	APEX BEAT 0		1		2		3		CARDIAC IMPULSE ABSENT		PRESENT	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
10-20	15	21.2	24	33.8	10	14	22	31	38	53.5	33	46.5
21-30	35	31.8	32	29.1	15	13.6	28	25.5	60	54.5	60	45.5
31-40	39	42	24	25.7	18	19.3	12	13	74	79	19	21
41-50	54	61.3	15	17.3	8	9	11	12.4	73	82.9	15	17.1
51-60	52	60	17	20	8	9	10	11	67	77	20	23
61-80	29	51.6	11	20	8	14.2	8	12.2	45	80.3	11	19.7

TABLE V. WEIGHT GROUPS OF MALES

WEIGHT (LBS.)	APEX BEAT 0		1		2		3		CARDIAC IMPULSE ABSENT		PRESENT	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
100-120	5	25	6	30	4	20	5	25	9	45	11	55
121-140	32	45.9	19	27	6	8.6	13	18.5	46	65.7	24	34.3
141-160	100	60.3	34	20.5	16	9.6	16	9.6	129	77.7	37	22.3
161-180	105	78.3	14	10.5	5	3.7	10	7.5	123	91.8	11	8.2
180-	90	85.7	6	5.8	1	0.9	8	7.6	97	92.4	8	7.6

TABLE VI. WEIGHT GROUPS OF FEMALES

WEIGHT (LBS.)	APEX BEAT 0		1		2		3		CARDIAC IMPULSE ABSENT		PRESENT	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
100-120	88	20.7	61	33.2	35	19.1	50	27	101	54.9	83	45.1
121-140	58	37.2	45	28.9	24	15.4	29	18.5	108	69.2	48	30.8
141-160	53	63.9	14	16.9	8	9.6	8	9.6	73	88	10	12
161-180	41	68.4	8	13.4	7	11.6	4	6.6	50	83.3	10	16.7
181-+	19	86.5	1	4.2	2	9.3	0	0	21	95.4	1	4.6

2. The overall demonstrability of the apex for all ages and weights, and both sexes, is only 24.6 per cent instead of the implied 100 per cent.

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Clinical Reports

PERIARTERITIS NODOSA

Report of Case

Captain John C. Eagan, M.C.

BECAUSE of the recent interest in periarteritis nodosa and the striking features in this case, the following report is presented:

CASE REPORT

A married white man, aged 37 years, was admitted to the Station Hospital, Fort Snelling, Minnesota, March 6, 1944, complaining of a pain in the left side of the chest, nonproductive cough, backache, fever, muscle, aching, and stiffness of leg muscles. The past history was negative. The patient denied infection with venereal disease. The family history was negative except for the fact that his father died at the age of 70 years from arteriosclerosis.

The patient stated that he had been sick with a cold for a week prior to his admission to the hospital. During this period he had perspired freely at night. At the time of admission, the patient complained of a pain throughout the left side of his chest, dry nonproductive cough, backache over the renal area, and extremely painful arm and leg muscles which he described as being stiff. Any movement of the muscles gave him considerable discomfort. He complained of feeling extremely tired and weak.

Physical examination revealed a temperature of 100° F., pulse rate, 96 per minute; respirations, 20. The breath sounds were increased throughout the left side of the chest and a few scattered râles were heard throughout the left side of the chest, posteriorly. The blood pressure measured 106/70. The examination of the heart was negative. There was tenderness of the forearm and the calf muscles. A roentgenogram of the chest taken March 9, 1944, showed no abnormalities in the lungs.

Laboratory examination showed 12,550 leucocytes per cubic millimeter; hemoglobin (Sahli) 89 per cent; neutrophiles, 70 per cent; lymphocytes, 28 per cent and eosinophiles, 2 per cent. The urine specific gravity was 1.020, with an acid reaction. It was negative for albumin and sugar. The sediment was normal. The blood Kahn was negative. The sedimentation rate of the blood was 50 mm. in one hour.

A tentative diagnosis was made of rheumatoid state or influenza.

On March 22, 1944, the patient continued to complain of extreme weakness of the leg muscles and he also complained of substernal pain. The temperature curve was irregular with variations from 100° to 102.6° F. The pulse rate was 90 to 100. The patient became constipated and required the use of laxatives and enemas. He stated that he did not have strength enough to move his bowels. The weakness became more marked. Blood cultures were taken and reported as negative. Blood counts showed 4,500,000 erythrocytes per cubic millimeter, 17,900 leucocytes per cubic millimeter, and hemoglobin (Sahli) 85 per cent. The differential blood count was reported as neutrophiles, 82 per cent; lymphocytes, 17 per cent; eosinophiles, 1 per cent.

On March 27, 1944, after a trial of salicylates with no apparent results, sulfadiazine was administered. No effect was noted on either the patient's well-being nor the fever.

On March 29, 1944, the test for heterophile antibodies was negative. There were no agglutinins for typhoid, paratyphoid, tularemia, or undulant fever in the blood serum. The blood serum proteins were: total, 5.65 Gm.; albumin, 3.59 Gm.; globulin, 2.06 Gm. per 100 cubic centimeters. The spinal fluid was clear, with 2 leucocytes per cubic millimeter; sugar, 61 mg. per cent. The Wassermann test was negative, and the colloidal gold curve was reported as 0000000. The test for globulin was negative.

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On March 31, 1944, the leucocyte count was 21,250 per cubic millimeter. The hemoglobin was 85 per cent (Sahli). The neutrophiles were 92 per cent and the lymphocytes were 8 per cent.

Repeated sputum examinations were negative for tubercle bacilli and *Monilia*. A stereogram of the chest on April 3, 1944, showed a decreased radiolucency in the right lower lung field in the region of the cardiohepatic angle which extended out from the lower portion of the right hilum to the costophrenic angle, suggestive of early pneumonitis. The heart was more transverse and appeared to be somewhat larger, both to the right and to the left. The transverse diameter of the heart was 16.2 centimeters. The transverse diameter of the chest was 32.7 centimeters.

On April 3, 1944, all sulfonamide therapy was stopped and 10 Gm. of sodium salicylate were given intravenously. The patient noted a marked ringing in his ears but seemed to obtain considerable relief. He stated that he felt much better and could raise his arms and legs without pain. Sodium salicylate, 160 grains, was given each day. The electrocardiographic findings were: auricular rate, 120 per minute; ventricular rate, 120 per minute; regular rhythm; P-R interval 0.20 second; QRS interval, 0.06 second; R-T interval, 0.24 second. Impression: sinus tachycardia.

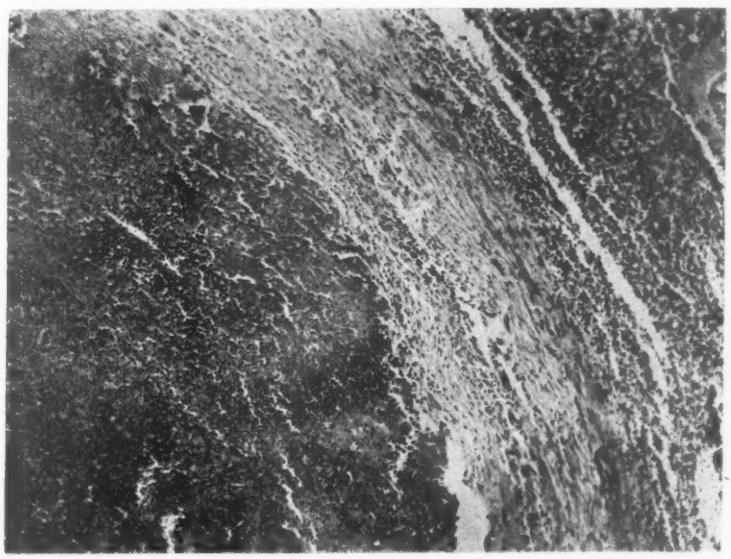

Fig. 1.—Wall of a coronary artery showing a thrombus in the lumen with massive periarterial exudate and thinning, resulting in destruction of the wall of the artery. (Magnification, ×100; hematoxylin-eosin stain.)

On April 9, 1944, the patient noticed a numbness and tingling in the ulnar distribution of the right forearm and hand. A marked weakness of the right arm was also noted. He stated that he was unable to raise his right or left arm. The patient had been losing weight rapidly and had been unable to rest at night. Vitamin B_1 was given parenterally.

On April 15, 1944, an enlarged, extremely tender node was found in the right axilla. Several small nodular masses were noted along the lateral margin of the right tibia; these seemed to be attached to the vessel. The clinical diagnosis was changed to periarteritis nodosa.

A nodule was removed and sent to the Department of Pathology of the University of Minnesota. The pathologist confirmed the diagnosis of periarteritis nodosa from the biopsied nodule.

On April 25, 1944, weakness and numbness were noted in the left forearm and hand. There was progressive loss of weight. More nodules were noted in the left arm. Penicillin therapy was started by intravenous route and continued intramuscularly. On April 30, 1944, the patient suddenly complained of a headache and could see only large objects; he became comatose. The reflexes on the left side were diminished; the reflexes on the right side were exaggerated. The clinical impression was probable involvement of a cerebral vessel or uremia. The patient had several convulsive seizures and became very

cyanotic. Urinalysis was negative. The fluid intake was accomplished by administration of fluids intravenously. On May 2, 1944, little change was noted except an inability to respond to questions. On May 3, 1944, he seemed more alert, the vision was clearer, and he was able to recognize both objects and people. About midday he started to hiccup, cyanosis developed, the breathing ceased, the head dropped to the left, and the patient expired on the fifty-eighth day of hospitalization.

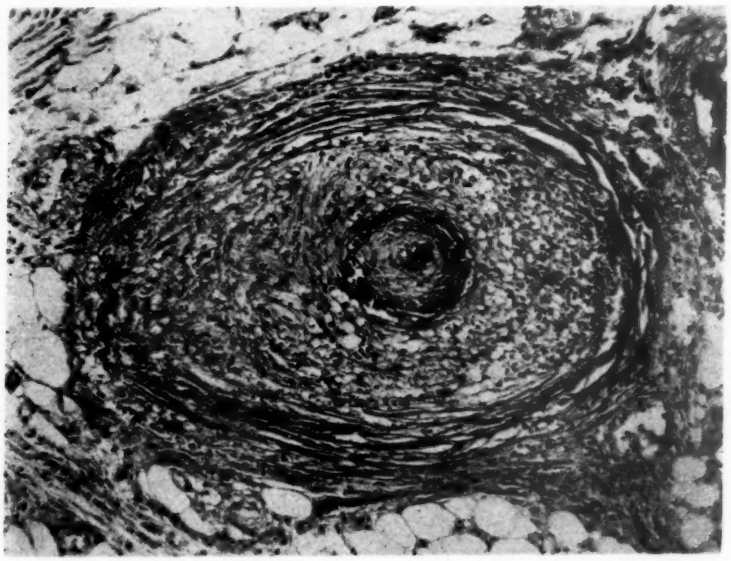

Fig. 2.—Artery of the cutis showing marked thickening of the intima with characteristic band of hyaline near the lumen and cellular exudate throughout all layers of the artery. (Magnification, ×65; hematoxylin-eosin stain.)

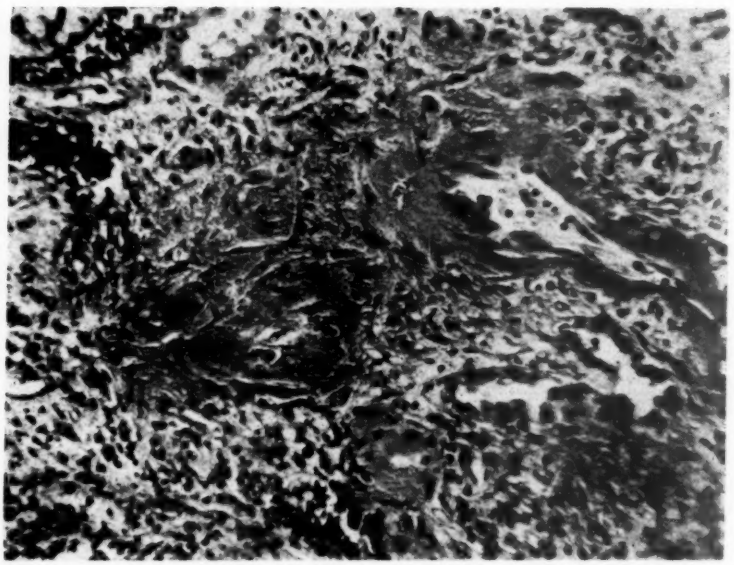

Fig. 3.—An artery in the kidney showing characteristic hyaline degeneration of the intima and a moderate amount of inflammatory exudate in the adventitia. (Magnification, ×150; hematoxylin-eosin stain.)

NECROPSY FINDINGS

Subconjunctival petechiae were present in the conjunctiva of the right eye. The pericardial sac contained an increased amount of fluid. The heart weighed 475 grams. There was left ventricular hypertrophy. The anterior descending branch of the left coronary artery was partially occluded in its proximal third by a thrombus (Fig. 1). The spleen

weighed 300 grams. There was thrombosis of the splenic vein. Multiple infarcts were found in the spleen. An artery of the cutis, taken from the abdominal wall, showed marked thickening of the intima with a characteristic band of hyaline near the lumen, and cellular exudate throughout all layers of the artery (Fig. 2).

Liver: Weight, 2,350 grams. Numerous small aneurysms were found in the intrahepatic arteries.

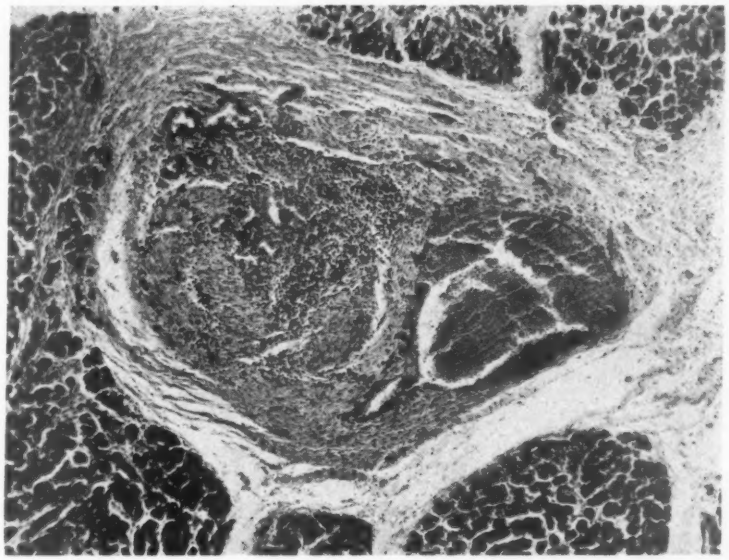

Fig. 4.—An artery in the pancreas showing inflammation in the artery with exudate from lumen to adventitia. (Magnification, ×65; hematoxylin-eosin stain.)

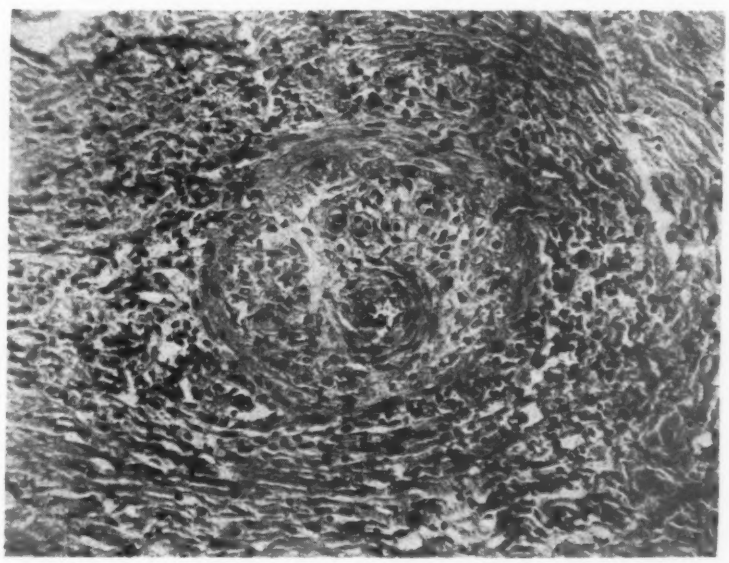

Fig. 5.—A small artery showing massive periarterial exudate and an organized thrombus in the intima. (Magnification, ×150; hematoxylin-eosin stain.)

Gastrointestinal tract: A superficial ulcer was found on the lesser curvature of the stomach. A small aneurysm was noted in the mesenteric artery supplying the jejunum.

Kidneys: The right weighed 225 grams; the left weighed 250 grams. Both kidneys showed sunken areas on their surfaces. The centers were pale and the margins were hemorrhagic. There were subcapsular petechiae in both kidneys. Petechial hemorrhages were present in the pelvis of the right kidney (Fig. 3). An artery in the pancreas showed

inflammation with exudate spread from the lumen through to the adventitia (Fig. 4). A small artery showed massive periarterial exudate and an organized thrombus in the intima (Fig. 5). Several enlarged periaortic lymph nodes in the region of the common duct were found. Subperiosteal petechiae were found on the calvarium.

COMMENT

According to Bell[1] periarteritis nodosa is an inflammatory lesion affecting the medium-sized and small arteries in various parts of the body. The anatomic feature is the presence of the nodular thickenings of the arteries which represent small thrombosed aneurysms. Nodules are most easily observed on the coronary and mesenteric vessels; usually they are only a few millimeters in diameter and appear as firm, rounded, whitish masses, separated by segments of normal artery.

The initial lesion seems to be an injury of the media with the formation of hyaline necrotic tissue. This is soon followed by cellular infiltration of the walls with mononuclear leucocytes, eosinophiles and polymorphonuclear leucocytes. The infiltrate fills the adventitia of the vessel and may spread into the surrounding tissue. The small vessels usually become thrombosed. A weakening of the wall leads to the formation of a small aneurysm which usually becomes thrombosed, but may rupture. Small infarcts found in the kidneys cause renal insufficiency. Frequent abdominal pain is probably due to a closure of a mesenteric vessel. According to Bell[1] the cause of death may be uremia, hemorrhage, coronary thrombosis, or a cerebral accident.

Landis[2] describes periarteritis nodosa as a form of panarteritis accompanied by systemic symptoms of infection with added regional symptoms, depending on the organs involved. The specific agent is unknown, but suggested causes are streptococci, a filtrable virus, or allergy. Landis described a typical case with the onset being either insidious or violent with moderate fever, sweating, tachycardia, malaise, fleeting edema, progressive weakness, and accompanying diffuse, joint, muscular, or abdominal pain. There is secondary anemia with moderate to severe leucocytosis and, occasionally, conspicuous eosinophilia. The liver and spleen may be palpable. The muscles are usually atrophied and tender. The blood pressure may be elevated. In contrast to thromboangiitis obliterans, the visceral arteries are more frequently affected than the peripheral arteries.

Lichtman et al.[3] state that the possibility of periarteritis nodosa should be considered in young adults who present a picture of a febrile, very debilitating disease that may have an occasional exacerbation, with pain in the abdomen and extremities, anemia, albuminuria and hematuria, peripheral neuritis, loss of weight and with subcutaneous nodules.

The bizarre picture should place one on his guard, and by a process of elimination the diagnosis may be made. Many cases are featured by asthma and eosinophilia and signs of glomerular nephritis. These findings were not present in the case being reported. It is with regret that nothing can be added to the therapy or the etiology of periarteritis nodosa. In the opinion of this reporter, the disease is more common than previously realized.

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COMPLETE A-V BLOCK IN A FETUS

Case Report

Captain Robert K. Plant, M.C., and Major Robert A. Steven, M.C.

A WOMAN, aged 26 years, gravida i, Register No. 12187, was seen in the prenatal clinic at Torney General Hospital, Palm Springs, California, on Feb. 14, 1944. Her last menstrual period occurred on June 12, 1943, making her expected date of confinement March 19, 1944. Her pregnancy had been uneventful except for slight spotting which had occurred at the time of the third and fifth missed menstrual periods. The general physical and laboratory findings were essentially negative. The fundus extended 6 fingerbreadths above the umbilicus with the fetus in the left occipito-anterior position. The maternal heart rate was noted as 88 per minute, while the fetal heart rate was noted as 60, regular, and not affected by pressure on the fundus. The patient was observed at approximately weekly intervals until term, and at each visit the fetal heart rate was found to vary between 50 and 60 per minute. It was regular and not affected by pressure on the fundus. A flat roentgen film of the abdomen on March 3, 1944, disclosed no gross abnormalities of the fetus.

A fetal electrocardiogram on March 10, 1944, showed the fetal rate to be 56 and the maternal rate to be 74 per minute. The deflections due to the fetal heart showed no variation from normal in the short strips obtained (Fig. 1).

The patient delivered on March 20, 1944, after a fifty-nine-hour labor. Prolonged labor was due to primary atony of the uterus. During labor it was noted that the fetal heart rate remained between 50 and 60 per minute and was not affected by labor pains. At birth, the child (Register No. 12242) was seen to be a well-developed male infant weighing 8 pounds 2¼ ounces and having a normal cry and respirations. The color was normal except for moderate cyanosis of the palms of the hands and the soles of the feet. This was not more severe than is often found in a newborn infant. An hour or two after birth the color of the nail beds was pink, and there was no cyanosis anywhere. The baby was not irritable or cross and breathing seemed easy and free. Examination of the infant's heart revealed the point of maximum intensity to be just medial to the midclavicular line, but pulsation could be felt in the epigastrium giving the impression that there was some cardiac enlargement. The rate was 52 per minute and the rhythm was regular with no variation with respirations. The heart sounds were normal. There was a soft, blowing systolic murmur in the left second intercostal space, near the sternum, which was not transmitted and which was interpreted as a physiologic murmur. X-ray examination of the heart showed gross cardiac enlargement. An electrocardiogram taken about three hours after birth (Fig. 2) showed complete A-V dissociation with a ventricular rate of 50 per minute and an auricular rate of 114 and marked right axis deviation.

The baby's weight dropped to 7 pounds 9 ounces on the third day of life and rose to 7 pounds 12 ounces about the sixth day of life. The baby did not nurse well. Pallor developed which gradually became more marked. On the morning of March 26, 1944, the infant developed definite cyanosis, and the liver was felt 2 fingerbreadths below the costal margin. Cyanosis rapidly became more marked, and at 2:00 P.M. the infant expired.

An electrocardiogram taken March 22, 1944, was identical with the first one except that the auricular rate had risen to 134 per minute, and a third tracing, taken on the day of death, showed an auricular rate of 150 per minute, with inversion of T_1 and T_4 (Fig. 3).

AUTOPSY REPORT

The autopsy was performed by Lieutenant Colonel Hans F. Smetana. Our brief extract from his report follows, giving only the pertinent findings but including in toto the microscopic examination of the heart:

The heart was grossly enlarged, weighing 56 grams (normal, 20.6 grams) and had flattened the lungs, especially on the left, posteriorly and laterally against the rib cage. The

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ductus arteriosus appeared closed. No septal defects were present and the valves were normal. The distribution of coronary vessels was normal. The pulmonary conus was quite large.

The lungs showed extensive atelectasis and early bilateral bronchopneumonia. There was passive hyperemia of the spleen, liver, kidneys, and brain. The liver extended 4 cm. below the costal margin. There was some hemorrhage into the meninges and a small hematoma in the galea aponeurotica in the occipital region, presumably due to forceps.

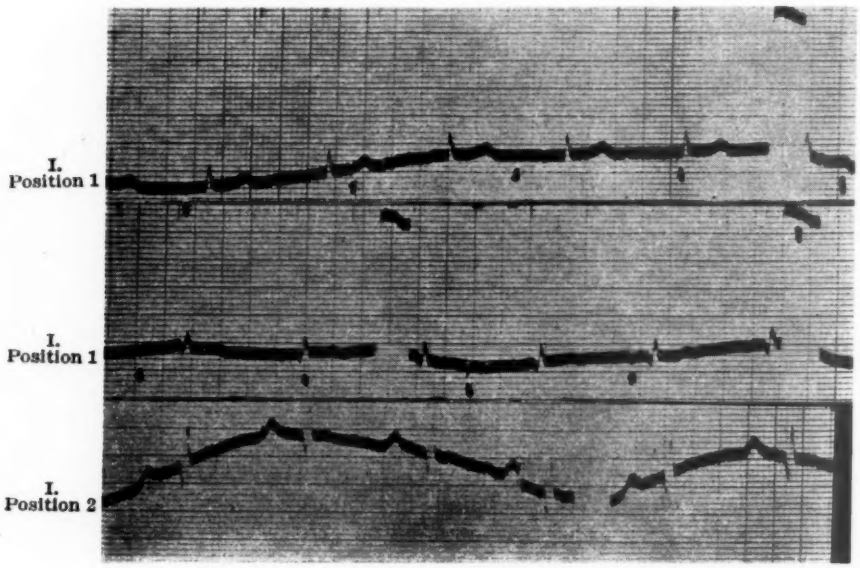

Fig. 1.—Electrocardiogram taken March 10, 1944.

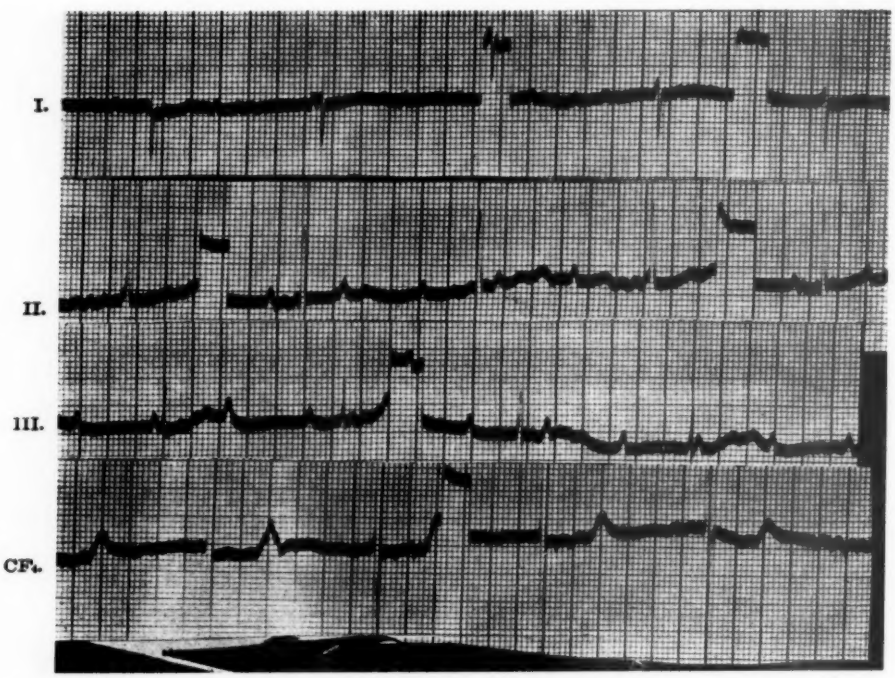

Fig. 2.—Electrocardiogram taken March 20, 1944.

Heart.—Section A: This is a cross section through the interventricular septum just beneath the membranous septum and includes parts of the walls of the right and left ventricles. The endocardium of the septum facing the right ventricle is of normal thickness

and shows no Purkinje fibers of the bundle of His. The myocardial fibers of the septum and of the wall of the ventricle are of normal size. Their cross striations can just be made out. The endocardium facing the left ventricle is thicker than that on the right and the borderline between it and the myocardium is somewhat irregular. Halfway between the endocardial surface and the myocardium are a few strands of muscle fibers with abundant fibrillae showing cross striations which are as definite as those of the fibers of the myocardium. These strands, however, are separated from the main myocardium by rather dense collagenous fibrous tissue. There is moderate congestion of the capillaries of the myocardium especially in the left superficial layers of the septum and minute hemorrhages seem to have occurred. There is no inflammatory reaction. The epicardium is not remarkable. The vessels in the subepicardial fat tissue appear normal. *Phosphotungstic acid stain:* The subendocardial muscle fibers show a normal fibrillar arrangement with cross striations. Some of these fibers appear vacuolated. The fibrillar structure of the myocardial fibers appears normal.

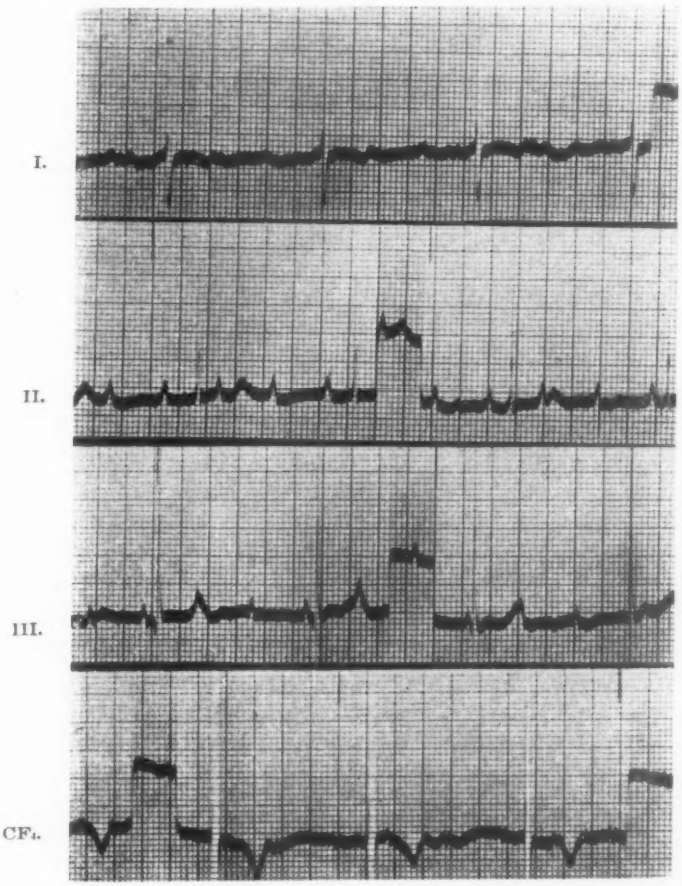

Fig. 3.—Electrocardiogram taken March 26, 1944.

Section B: This is a section through the prominence on the anterior surface of the heart and includes the interventricular septum. No Purkinje fibers are recognized in the endocardium on either side of the septum. A few groups of muscle fibers beneath the endocardium facing the left ventricle are separated from the main myocardium by a fibrous band but the character of the fibers is not that usually encountered in the bundle of His. There is no inflammatory reaction. The peculiar and complicated character of the pulmonary conus is well brought out in this section. The myocardum appears normal. The epicardium is normal. *Phosphotungstic acid stain:* There is no significant difference in the structure of the myocardial fibers beneath the endocardium from those of the main myocardium. *Best's carmine stain:* No glycogen-containing fibers are seen beneath the endocardium of the interventricular septum on either side nor within the main myocardium.

Aorta.—The aorta is normal.

AUTOPSY SUMMARY

At autopsy the most outstanding finding was a very large heart causing compression of both lungs with partial atelectasis. No gross structural defects were noted in the heart and there were no congenital malformations except a large pulmonary conus. In order to be able to demonstrate possible changes of the bundle of His the entire heart was fixed in formalin saturated with dextrose to preserve the glycogen of the Purkinje fibers. Frozen sections as well as paraffin sections, taken from the septum of the ventricles, failed to show subendocardial fibers which can be identified as Purkinje fibers. Since there is no septal defect, the complete heart block is tentatively attributed either to absence or faulty development of the bundle of His. The enlargement of the heart is considered to be secondary to the slow heart rate resulting in anoxemia.

Death is attributed to the circulatory failure and partial atelectasis of the lungs complicated by early bronchopneumonia. The birth trauma of the brain, as demonstrated by the meningeal hemorrhages and cellular infiltrations over the left occipital lobe, is perhaps a contributory factor.

COMMENT

No discussion of fetal electrocardiography is intended or necessary here. There is a fairly extensive literature on this subject. Suffice it to comment that to date the only information to be gained from a fetal tracing is determination of the cardiac rate or, in the case of multiple pregnancies, rates. This has been made practical largely through the use of amplifiers. The authors were using the Sanborn cardiette but were able to get only an amplification of 2.5 times instead of the anticipated 6 times; as a result the deflections were quite small but nevertheless clearly discernible. Lead I wires were used. Electrodes were placed in the epigastrium and the right lower quadrant for Position 1. Several other positions were used but no deflections obtained.

From the examinations of frozen and paraffin sections noted, it appeared that the cause of the block was an absence or imperfect development of the bundle of His. Further studies were carried out by the Army Medical Museum. The letter from the Museum, signed by Lieutenant Colonel Balduin Lucke, Deputy Curator to the Chief of Laboratory Service, Torney General Hospital, follows:

"1. We are in agreement with your findings in the interesting case of G.D.G., your #51, A.M.M. Acc. 109014. Additional blocks were cut from the material submitted, and we have been unable to identify with any certainty the fibers of the conduction system. We believe that the heart block consequently must be related to the maldevelopment of the conduction system."

To the authors' knowledge, complete heart block has not been recognized in utero before. The slow rate plus the failure of the rate to vary with uterine contractions led us to feel that we were dealing with complete A-V dissociation.

ANNULUS FIBROSUS CALCIFICATION OF THE MITRAL VALVE

NATHAN BLOOM, M.D., AND GRACE CASHON
RICHMOND, VA.

CALCIUM deposition in diseased heart valves may be demonstrated frequently in necropsy studies, but these deposits are usually overlooked clinically unless the heart is carefully examined roentgenographically. Sosman[1] discusses in detail a simple method of demonstrating the presence of calcific deposits within the heart by x-ray. He suggests a small fluoroscopic aperture and a screen of high intensity, using a 5-inch gap and 5 ma., to locate the calcified valves. The patient is rotated into a slight anterior right oblique position, about 15 to 20 degrees; then the examiner looks through the heart along the line of the auriculoventricular sulcus. This region can be identified by finding the auriculoventricular junction on the left border and searching obliquely across the heart shadow downward and medially, 45 degrees from the horizontal from this point. In this position, both the aortic and mitral valve calcifications are best seen, but they are difficult to differentiate. If intracardiac calcification is found, the patient is rotated to the left anterior oblique position. In this position, the mitral valve is in the posterior third of the heart shadow, while the aortic valve is in the mid-third. The valves will show up as dense irregular nodular masses, similar in appearance to calcified mesenteric glands, and they are darker shadows within the dark heart shadow. Rings of fibroelastic tissue at the roots of the cardiac valves, known as the annuli fibrosi, may become calcified and appear as a solid mass, having a J-shaped or U-shaped appearance. This is usually considered a senile change, associated with other evidence of senility, such as Mönckeberg's sclerosis, arcus senilis, and calcified intervertebral discs. It is associated very seldom with organic heart disease. This particular case is presented because of the finding within the heart of a large calcified mass, apparently not associated with any demonstrable evidence of organic cardiac disease.

CASE REPORT

History.—A white man, aged 38 years, complained of indigestion for several years. In April, 1944, he was referred to Dr. Fred Hodges for a gastrointestinal x-ray study. This proved to be negative, but during the investigation a deposit of calcium was demonstrated within the heart. The patient had never complained of any cardiorespiratory difficulty, but during a superficial examination in 1939, was told that he had a heart murmur. His childhood had been uneventful except for frequent sore throat. There was no history of rheumatic fever or any other unusual ailments.

Physical Examination.—The patient was tall and spare, weighing 116 pounds and appearing much older than his stated age. There was a right divergent squint and opacities were evident in both optic lenses. There was moderate arteriosclerosis of the retinal vessels without hemorrhages or exudates. The patient had a marked kyphosis of the spine, involving the upper thoracic vertebrae. The lungs were clear. The blood pressure was 130/85 in both arms. The heart was not enlarged. There was a short systolic murmur, heard best at the apex and transmitted to the left axilla. There was no thrill. The pulmonic second sound was slightly accentuated. The aortic sounds were normal. The abdomen was soft and no masses were palpated. The radial arteries were moderately thickened. The extremities and reflexes were negative.

From the Department of Cardiology, Medical College of Virginia.
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Laboratory Studies.—The blood Wassermann test was negative. There was no sugar or albumin in the urine. The red blood count was 4,300,000 per cubic millimeter; the hemoglobin was 85 per cent (Sahli). An electrocardiogram was considered within normal limits, and a stethogram demonstrated a moderately intense systolic murmur at the apex.

Fluoroscopy.—The lungs were clear; the heart was small and in the mid-position. The right border was straight. The pulmonic conus was not enlarged. A large calcified mass was visible within the heart in all positions. This mass was situated along the margin of the left ventricle in the region of the mitral valve. In the left oblique position the mass was more prominent, lying posteriorly in a semilunar curve, 7 cm. in length and about 6 mm. in diameter. The mass moved within the heart at each pulsation.

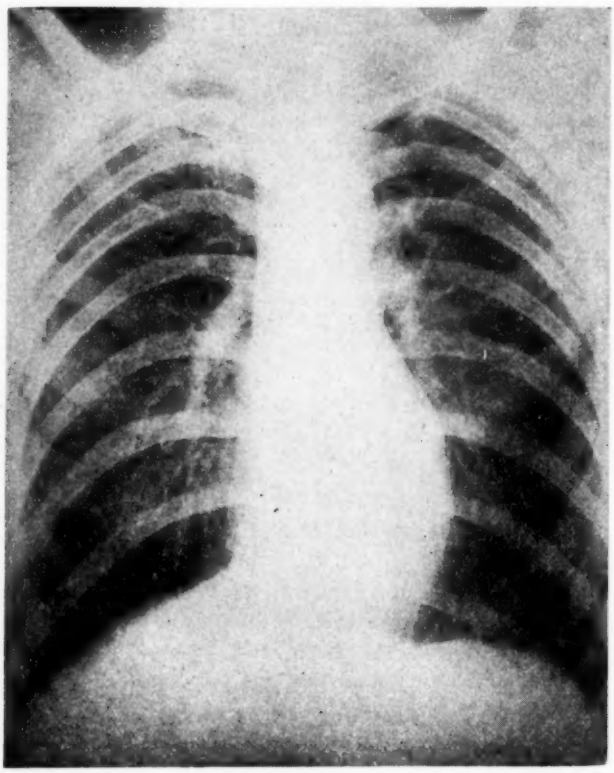

Fig. 1.

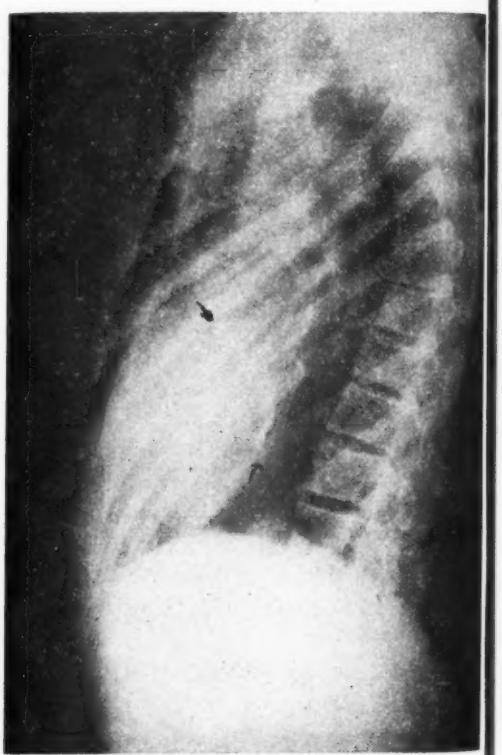

Fig. 2.

Fig. 1.—Calcification of mitral annulus fibrosus. Roentgenogram of chest, posteroanterior position. A small heart with straight right borders. Calcified mass within the left ventricle.

Fig. 2.—Calcification of mitral annulus fibrosus. Roentgenogram of chest, left lateral position; calcified semilunar mass in posterior third of the heart shadow.

DISCUSSION

Intracardiac calcification is not rare. There have been many studies concerning calcification within the heart, caused by arteriosclerosis or by superimposed deposits of calcium on rheumatic valves. It has been emphasized that deposition of calcium on the valves is characteristic of rheumatic heart disease.[2] It would seem wise to make a distinction between calcified valves and calcification of the annulus fibrosus. This is a rather difficult problem, as the annuli fibrosi lie at the bases of the valves, but Sosman[1] has shown that, when a valve becomes calcified, it appears as a group of small, irregular, nodular masses, but the annulus fibrosus calcification is a solid mass having a curved appearance. It is believed that in our case there is a calcified annulus fibrosus. The patient had generalized arteriosclerosis and bilateral cataracts and looked to be about 60 years of age, although he was only 38. There was nothing in the history suggestive of old rheumatic heart disease. The murmur at the apex was not con-

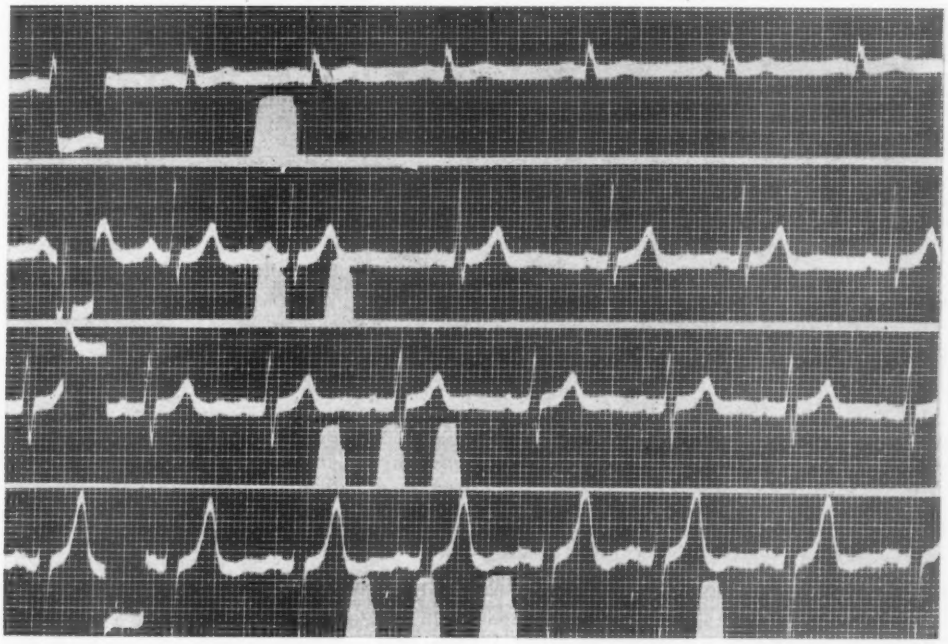

Fig. 3.—Calcification of mitral annulus fibrous. Electrocardiogram; the tracing was considered within normal limits.

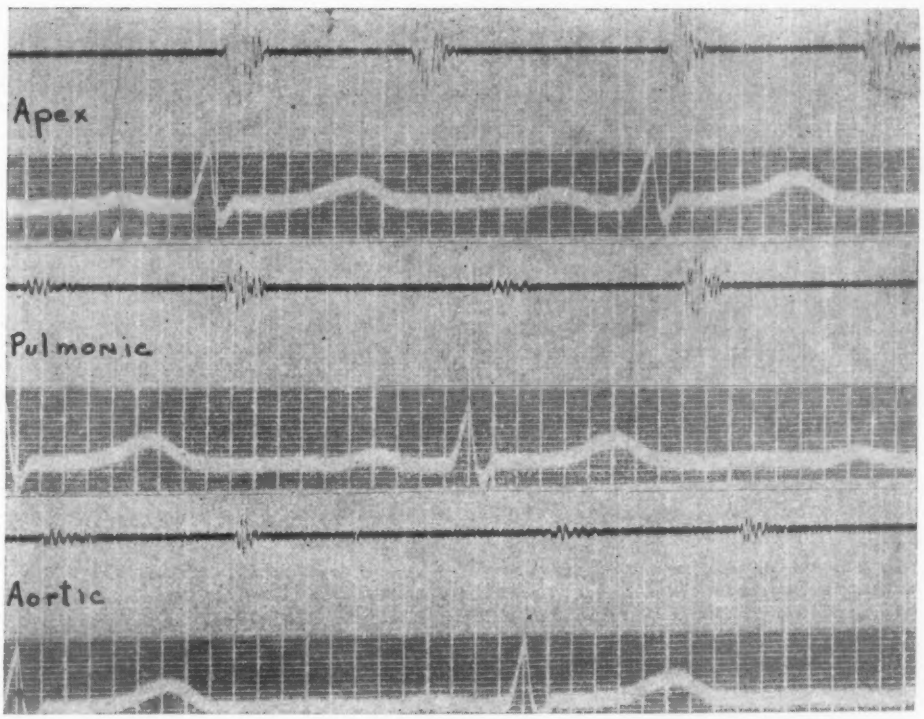

Fig. 4.—Calcification of mitral annulus fibrosus. Stethogram; the increased vibrations at the apex are considered as due to a soft systolic murmur.

clusive, and the heart itself did not have the contours usually seen in mitral valve disease. The intracardiac calcification in this man was probably a degenerative change due to premature senility.

CONCLUSION

Calcification within the heart may be demonstrated frequently by the fluoroscope. Knowledge of the type of calcification and the area involved aids considerably in the clinical diagnosis. This case is presented as one of calcification in the annulus fibrosus of the mitral valve.

We wish to thank Drs. T. N. Barnett and Fred M. Hodges for allowing us to report this case.

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CONTUSION OF THE HEART

A Case Report

Major Lewis K. Reed, M.C., and Captain Knute E. Berger, M.C.

THE following case of cardiac trauma due to a blow on the chest is of interest because it is possible to estimate the force producing the injury and to follow the electrocardiographic changes from shortly after the accident until complete recovery.

CASE REPORT

Present Illness.—The patient was a white aircraft mechanic, aged 26 years. At 4:30 P.M. on Dec. 11, 1943, he was helping four other men attach the trailer arm of a fully loaded, 2,000 gallon gasoline trailer to a tug. In lifting the arm above the horizontal to attach it to the pintle hook of the tug, the forward dolly to which the trailer arm was attached suddenly rotated, and the arm snapped upward, pinning the patient between the trailer arm and the bottom of the gas tank (Fig. 1). The patient cried out, became red in the face, and lapsed into unconsciousness. It required the concerted efforts of five men pulling down on the end of the trailer arm to lower it and release the patient. He was impinged for somewhat less than one minute and remained unconscious for about one and one-half minutes after release.* On admission to the hospital thirty minutes after the accident, the patient complained of weakness and steady precordial pain which did not radiate to the neck or arms.

Physical Examination.—The patient was a slender white man, 69 inches in height and 178 pounds in weight. On admission he was pale and moderately dyspneic but not cyanotic. His neck veins showed no distention, the trachea was in the midline. *Lungs:* The expansion was equal; there was no abnormality of percussion or auscultation. The respiratory rate was 30 per minute. *Heart:* No visible or palpable increase of precordial activity could be observed. The cardiac apex was 7.5 cm. to the left of the midsternal line in the sixth intercostal space. The right border was at the right sternal margin. The heart sounds were well heard and there were no murmurs audible. The rhythm was completely irregular. The apical

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*From weight and measurement data obtained on the trailer, calculations were made by a mechanical engineer indicating that the trailer arm, in its sudden upward swing, delivered an estimated force of approximately 2,000 pounds. This force was expended on the patient's chest, protected by a fleece-lined, leather flying jacket over the usual fatigue uniform and undershirt.

rate was 128 and the radial pulse was 88 per minute. The blood pressure was 110/60. *Abdomen:* Negative.

The clinical impression on admission was cardiac contusion with auricular fibrillation. The patient was given ¼ grain of morphine sulfate and placed on strict bed rest. The first electrocardiogram (Fig. 2) was taken about two hours after the injury. Roentgenograms of the chest the morning following the injury showed an apical pneumothorax representing about 3 per cent collapse of the right lung; the cardiac silhouette was normal; a flat roentgenographic film of the abdomen was negative.

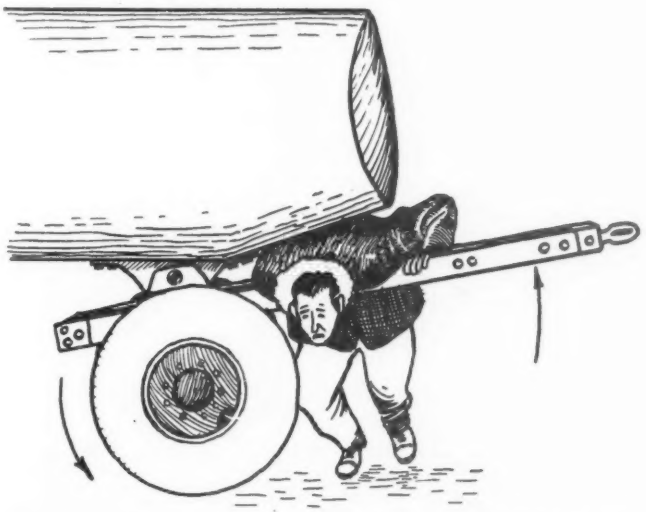

Fig. 1.—Illustration of manner in which the soldier was pinned between 2,000-gallon gasoline trailer and connector-tongue to tractor.

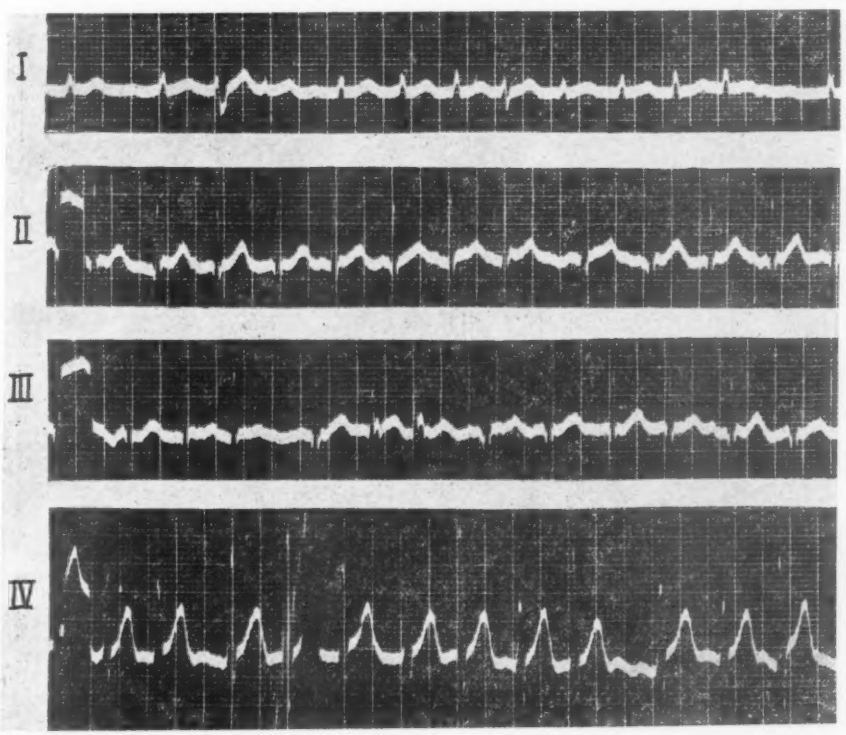

Fig. 2.—Electrocardiogram taken about four hours after injury. The variation in size of ventricular complexes indicates that auricular fibrillation is just ceasing or about to begin. There is an occasional ventricular premature beat, probably arising in the left ventricle (Lead I).

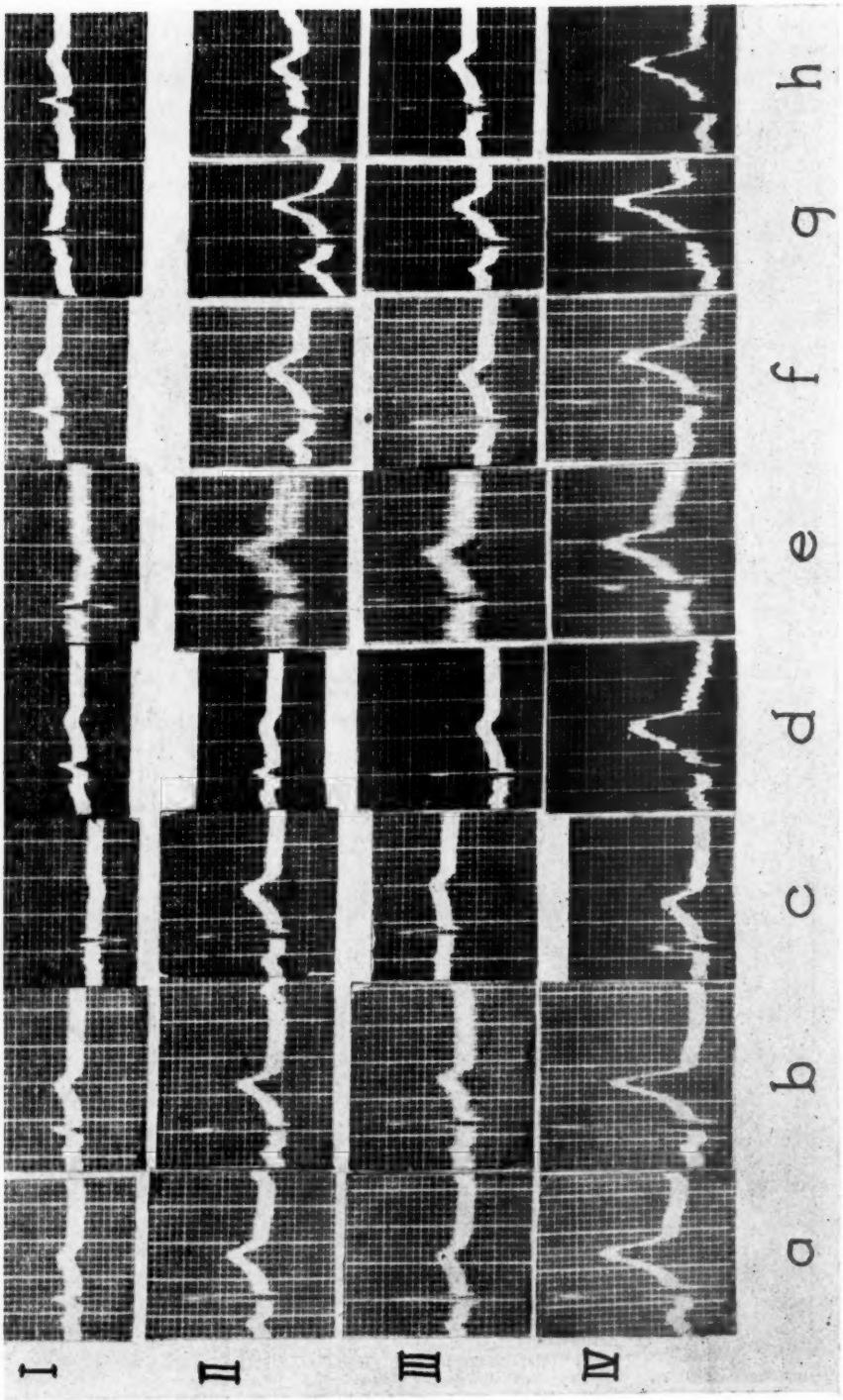

Fig. 3.—Serial electrocardiograms; *a* and *b* taken on Dec. 12 and 14, 1943, respectively, show no abnormality; *c*, Dec. 22, 1943, patient wheeled in chair to electrocardiographic laboratory and transferred to table. Electrocardiogram shows evidence of slight right axis deviation and mild right ventricular strain, acute; *d*, Dec. 24, 1943, patient in bed, electrocardiogram shows slurring QRS in Lead II, manifesting some myocardial damage; *e*, Dec. 31, 1943, patient returned to electrocardiographic laboratory by wheel chair, again the electrocardiogram shows some evidence of mild right strain; *f*, Jan. 8, 1944, patient in wheel chair, electrocardiogram normal; *g*, Feb. 4, 1944, patient ambulatory convalescent, again the electrocardiogram shows slight evidence of strain, no symptoms; *h*, Feb. 9, 1944, patient ambulatory, electrocardiogram normal. All subsequent records were normal.

Past History.—The patient had always been healthy, having had the usual mild, childhood diseases. He denied rheumatic fever, scarlet fever, renal or venereal disease and had always had good exercise tolerance with no cardiorespiratory symptoms. On the day preceding the accident he had undergone a complete, routine physical examination to determine his fitness for overseas duty. The pertinent findings at that time were: "Heart, normal; blood pressure, 130/84; pulse, sitting, 80; pulse, immediately after exercise, 100; character of pulse, normal; arteries, normal; blood Kahn test, negative; urinalysis, normal."

Hospital Course.—Clinical evidence of arrhythmia ceased about seven and one-half hours after admission. Serial electrocardiograms are shown in Fig. 3, the first of which (*a*) was taken about 9 A.M. the morning following the accident. On that day he had mild substernal pain, without exertion, and some difficulty in swallowing solid food. The heart sounds were well heard, the rhythm was regular, and the pulse was 90 with no deficit. During the first two days following the injury his temperature ranged from 99° to 99.6° F. after which time he remained afebrile during the entire convalescence. On the third day he developed some soreness on swallowing which he localized to the insertion of the right sternocleidomastoid muscle. Examination of the chest revealed a friction rub on deep inspiration along the upper portion of the right sternal border. This had disappeared on the following day, but he continued to have a pleuritic pain in the right side of the chest anteriorly. By the sixth hospital day he was clinically well. X-ray films at this time showed that the pneumothorax had disappeared. Throughout the convalescence the blood pressure ranged from 100 to 116, systolic, and 60 to 70, diastolic. There was never a significant difference in blood pressure between the two arms. On the day following admission the leucocyte count was 10,150 per cubic millimeter, with 62 per cent neutrophiles. Frequent counts thereafter revealed a rapid return to normal. Sedimentation rates done on the third, seventh, and nineteenth hospital days were 48, 38, and 10 mm. per hour, respectively. All urine specimens were normal.

The patient was kept in bed for four weeks. Despite orders, he got out of bed on the fourteenth and sixteenth hospital days. At these times he developed moderate palpitation but no pain or dyspnea. On the seventeenth hospital day he volunteered symptoms suggesting extrasystoles, and clinical examination proved the presence of this condition. It will be noted in Fig. 3 that in each instance when the patient was moved in a wheelchair to the electrocardiographic laboratory the record shows evidence of a mild degree of strain.

Following four weeks of bed rest the patient was up progressively with restriction of activity and was given a graded convalescent program with increasing exercise for a period of five weeks. During this period he occasionally complained of brief periods when his heart "seemed to skip a beat"; these were apparently not related to physical activity. During the latter five weeks in the hospital no examiner was able to find any irregularity at the times of examination.

Re-examinations at three and four months after the injury were completed and were entirely negative. The patient was able to do full duty without complaint.

COMMENT

Kahn and Kahn[1] pointed out, in 1929, that the position of the heart directly behind the sternum and adjacent cartilages exposes it to injury from non-penetrating trauma to the adjacent chest wall. They showed that cardiac arrhythmias, heart block, and even rupture of heart valves could occur in the absence of external injury to the chest. Bilderbeck[2] reported a rupture of the right auricle immediately due to a blow on the chest without any evidence of injury to the thorax. Bright and Beck[3] showed that patients with cardiac contusion may die of cardiac rupture, especially during the second week after injury when myomalacia exists. Beck[4] pointed out that cardiac rupture is a rare complication of cardiac contusion and that the heart muscle can tolerate an excessive amount of trauma as demonstrated in dog experiments. Moritz and Atkins[5] traumatized dog hearts and demonstrated, following contusion, single or multiple areas of focal hemorrhagic necrosis in the myocardium either at, or remote from, the site of trauma. This focal necrosis gives way to the formation of myocardial scars. Beck pointed out that, in the absence

of rupture, cases of cardiac contusion in general should be treated in the same manner as coronary thrombosis.

Many cases of direct and indirect cardiac trauma have been reported in the literature, but the protocols universally lack data as to the exact force applied and usually are wanting of electrocardiographic tracings taken immediately after the trauma, and complete histories and physical examinations prior to the injury are not given. In the case herein described the established 2,000 pounds' striking force applied to the patient's chest may seem disproportionate to the injury received. Undoubtedly a portion of this force was dissipated by the heavy fleece-lined jacket which he was wearing. Furthermore the force was distributed over the entire flat surface of the chest anteriorly and posteriorly. The resiliency of the chest wall in a person of this age further tends to dissipate the force of such an injury as was herein described.

CONCLUSION

1. This case study confirms the work of other authors in proving, beyond doubt, that the heart may be injured by external trauma without evidence of injury to the chest wall.

2. This case demonstrates that a force which would ordinarily be considered lethal when applied directly to the chest, can be survived.

3. This study confirms the accepted treatment of cardiac contusion, namely the treatment of coronary occlusion.

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Abstracts and Reviews

Selected Abstracts

Hoffmann, F., Hoffmann, E. J., Middleton, S., and Talesnik, J.: The Stimulating Effect of Acetylcholine on the Mammalian Heart and the Liberation of an Epinephrine-like Substance by the Isolated Heart. Am. J. Physiol. **144**: 189, 1945.

The injection of acetylcholine into the isolated atropinized hearts of dogs, cats, rabbits, and guinea pigs regularly causes an epinephrine-like effect, i.e., an increase of heart rate and amplitude, as well as a change of blood flow in the coronary vessels.

The positive ino- and chronotropic effects of acetylcholine are abolished by ergotamine, by curare, and by nicotine.

The pharmacological characteristics of the stimulating action of acetylcholine on the heart enables us to designate it as "nicotine-like."

In the perfusate of the isolated heart, it is possible to identify the presence of an epinephrine-like substance liberated when acetylcholine or nicotine is injected into the heart. Under the stimulus of these drugs the perfusate acquires an activity which can be demonstrated by its positive inotropic action on the hypodynamic frog heart and by a relaxing effect on the rectal cecum of the fowl and on the small intestine of the rabbit.

AUTHORS.

Lawson, H., and Rehm, W. S.: The Effect of Hemorrhage and Replacement on the Apparent Volume of Plasma and Cells. Am. J. Physiol. **144**: 199, 1945.

No evidence was obtained for an increase in the rate of disappearance of the dye T-1824 during almost complete exsanguination or in the four-hour period following reinjection of blood, in experiments on barbitalized dogs. Indirect measurement of circulating plasma volume during exsanguination therefore seems legitimate. Such measurements indicated that fluid was added to plasma at the mean rate of 0.154 ± 0.0114 c.c. per kilogram per minute when blood was drawn at the rate of 2 c.c. per kilogram per minute until mean arterial pressure fell below 20 mm. of mercury. When the animals were kept alive by reinjection of blood and were bled to death at the same rate four hours later, the rate of plasma replenishment during the second bleeding was only 0.088 ± 0.0119 c.c. per kilogram per minute. The rate of addition of fluid to plasma was usually increased at the time when arterial pressure began to decline steeply during the bleeding.

Evidence was obtained that the circulating cell volume is overestimated by an average of about 29 per cent if it is calculated from the plasma volume and the hematocrit in drawn blood. When measured by this method, the gain in circulating cells following injection was about 29 per cent greater than the volume injected; and the loss during bleeding was about 29 per cent greater than the volume withdrawn. The percentage error sems to remain fairly constant throughout all stages of exsanguination. The error appears in most cases to be completely masked during the first bleeding in our experiments, presumably by expulsion of cells from the cell reservoirs.

AUTHORS.

Black, W. A., and Karpovich, P. V.: Effect of Exercise Upon the Erythrocyte Sedimentation Rate, Am. J. Physiol. **144**: 224, 1945.

1. Fifty aviation cadets, convalescing from upper respiratory infection, were given five minutes of strenuous exercise (the Harvard step-up test).

2. Blood samples were taken immediately before exercise, and half an hour, five hours, and twenty-four hours after exercise. The erythrocyte sedimentation rate was determined by the Westergren method.

3. Five minutes of strenuous exercise caused a variable effect upon the individual sedimentation rate. However, in the group tested there was a statistically significant increase

in erythrocyte sedimentation rates five hours after exercise but no significant change either half an hour or twenty-four hours after exercise. This indicates that the change is not lasting.

4. Post-exercise observations in no case showed any clinical manifestations of ill effects.

5. Data on thirty-nine subjects showed that there was no relation between the erythrocyte sedimentation rate before exercise and the score obtained on the Harvard step-up test ($r = -0.15$).

6. The contradictions regarding the effect of exercise upon the erythrocyte sedimentation rate found in the literature may be explained by the difference in the intensity of exercises and in the time of taking the blood samples. AUTHORS.

Lepera, L., and Pataro, F. A.: Normal Mean Zone of Values of the Precordial QRS in Normal Subjects, Rev. argent. de cardiol. **12:** 26, 1945.

In 100 normal persons a study was made of the mean value and the standard deviation of the QRS duration and of the voltage of its waves in precordial leads CF_1 to CF_6 arriving at the following conclusions:

The greatest mean value of QRS duration was 0.088 seconds in lead CF_2 the normal range being from 0.078 to 0.098 seconds.

The greatest mean value of Q resulted in CF_6 (1.3 mm.), the normal range being from 0.1 to 2.5 millimeters.

It was also in lead CF_5 where the greatest mean value of R voltage (12 mm.) was observed with normal limits between 6 and 18 millimeters.

Concerning the deepness of S its greatest mean value was observed in CF_2 (20.9 mm.), the normal values ranging from 15.8 to 26 millimeters.

In all cases the normal values were calculated on the basis of the mean value and the standard deviation. The wide variations of the latter are discussed. AUTHORS.

Schill, E.: Sinus Extrasystole With Consecutive Disturbance of Conduction in the Total Conduction System, Cardiologia **6:** 271, 1942.

Description and analysis of a case in which, in consequence of sinus extra systoles, a disturbance of the stimulus conduction between sinus and auricle as also between auricle and ventricle, corresponding the Wenckebach period, was observed. The deviation of the atrioventricular conduction periods from the known Wenckebach periods is caused by the extra auricle waves, which occur in ever shorter periods, a condition which is to be explained by the oft repeated demands and consequent deterioration of conduction between sinus and auricle in the sense of the Wenckebach periods. In other words, the functional disturbance of two functionally and spatially coordinated parts of the stimulus conduction system does not reveal itself spontaneously and independently, whereby the disturbance of the upper situated part of the phenomena influences the functional disturbances of the lower situated part. In consequence of the increased number of extra systoles in a short time and the consequent greater demands, the intraventricular condition was also disturbed. Fundamental for the phenomena described is the not intact, only by low frequence normally functioning stimulus condition system. The cause of the trouble in the stimulus conduction system is unknown, most probable in sclerosis of the corresponding artery. AUTHOR.

Saphir, O.: Laryngeal Edema, Myocarditis and Unexpected Death, Am. J. M. Sc. **210:** 296, 1945.

Five children who rapidly developed symptoms of upper respiratory obstruction and succumbed quickly, despite tracheotomy, are recorded. Autopsies disclosed severe laryngeal edema, edema of the epiglottis and subglottic area, and acute myocarditis. The edema is interpreted as an early stage of so-called laryngotracheobronchitis. The unexpected death was probably caused by myocarditis. If the attending physician in future instances is aware of this complication, supportive measures might forestall the fatal outcome. AUTHOR.

Moguel, R. B.: Histologic Structure of the Valvular Endocardium, Arch. Inst. cardiol. México **15:** 113, 1945.

A study of the cardiac valves in the normal adult was undertaken, in which aniline techniques were used to stain the elastic fibers and argentic impregnation of the precollagen structure; this resulted in the discovery of the following unpublished data.

All cardiac valves, beneath the endothelium, have a layer of extremely thin, rectilinear filaments of precollagen, slightly or not at all ramified, usually running in a single direction

that form something similar to a basal membrane that offers support to thick elastic nets.

The spongiosa contains flexuous filaments that have a tendency to form ringlets and are slightly acidophilous; they must be considered as formed by a substance with characteristics intermediate between precollagen and collagen. This spongiosa, in all appearances, constitutes the most active component of the cardiac valves.

The fibrosa constitutes the skeleton of the valvular membranes and is made up in its entirety of very thick and rigid fasces of collagen.

The basal membrane reaches a greater development in the auriculoventricular valves than in the sigmoids and is reinforced by filaments of considerable thickness that lie athwart them. The subendothelium also has a reinforcement consisting of rigid strands of precollagen intermingled with elastic nets.

The spongiosa of the atrioventricular valves is polymorphous: near the base of implantation it has features which resemble those of the basal membrane, whereas toward the center the precollagenous filaments present soft undulations and tend to run in a single direction so as to reach the free edge in the form of long regularly flexuous and very lax curls; furthermore, the spongiosa of the auriculoventricular valves contains many anastomosed cells with a polyblastic capacity.

The fibrosa of the atrioventricular valves differs from that of the sigmoids due to its heterogeneous nature. At the base of implantation the faces of collagen are dense and run in a single direction, whereas around the free edge the bundles intercross, frequently dissociating, all of which forms lax spaces in the zones comprised among the tendinous insertions.

No great variations are specified in the filamentous structure of the cardiac valves because those encountered do not present sufficient regularity and one has the impression that many of them may be pathologic.

All the fine argentophile fibers, especially the flexuous and slightly acidophilic ones of the spongiosa, are susceptible of transformation during inflammatory processes into thick, retractile, collagenous bundles. They are responsible for the main deformities found in abnormal valves.

Some of the elastic fibers of the cardiac valves, notably the finer ones, may under certain circumstances, take a silver stain; it is possible that such argentophilia may denote a morphogenetic relationship between these elastic fibers and the precollagenous structure.

AUTHOR.

Berconsky, I., and Cossio, P.: Pain in Epistenocardia Pericarditis, Rev. argent. de cardiol. **12:** 1, 1945.

Based in clinical experience the authors claim that the epistenocardial pericarditis (post-infarction pericarditis) may account for the painful episode (acute or dull pain) which occurs sometimes one or two days after myocardial infarct.

This painful episode has its own qualitative and occasional peculiarities; for instance, its exacerbation by a deep inspiration, a circumstance which allows the prediction of friction rubs and eliminates the possibility of new infarctions. The authors recommend its control with amidopyrine or acetylsalicylic acid rather than morphine, unless the pain becomes intolerable. The characteristics of the pain and its diagnostic and therapeutical importance are made objective by a short account of three personal observations. AUTHORS.

Watson, R. F., Rothbard, S., and Swift, H. F.: The Relationship of Postscarlatinal Arthritis and Carditis to Rheumatic Fever, J. A. M. A. **128:** 1145, 1945.

The purulent complications and nonpurulent sequelae which occurred among 110 cases of scarlet fever in young adults who were intensively studied were analyzed. Group A streptococci, representing at least thirteen different types, were recovered on culture of the nasopharynges of 109 patients and a group C strain from the remaining one. Antistreptolysin O and antifibrinolysin titrations were made with the serums and plasmas, respectively, for all patients at weekly intervals.

Sixty-three patients had uncomplicated infections and made uneventful recoveries; twenty-nine suffered purulent complications; and twenty-two, including four who also had purulent complications, developed pronounced and unequivocal electrocardiographic abnormalities comparable with those seen in patients with active rheumatic carditis. Three of these twenty-two patients developed abnormal electrocardiograms during their acute streptococcic infection and the other nineteen during postscarlatinal convalescence. It is this latter group of nineteen patients who are of particular interest in this study.

Eight of the nineteen patients who developed electrocardiographic abnormalities during postscarlatinal convalescence had definite clinical attacks of rheumatic fever of varying severity. Four others differed from these eight in that their rheumatic-like manifestations were milder and more transitory. The remaining seven during a comparable period in their convalescence developed similar electrocardiographic abnormalities without other symptoms of rheumatic fever, although several had brief secondary rises in temperature, leucocyte count or erythrocyte sedimentation rate. The difference between these three groups of patients is quantitative rather than qualitative, and we believe that all suffered from the same fundamental tissue injury following their streptococcic infection; namely, that characteristic of rheumatic fever. AUTHORS.

Martiarena, L. H.: Secondary Tumor of the Heart Diagnosed at Operation, Rev. argent. de cardiol. **12:** 13, 1945.

A case is reported of secondary heart tumor with clinical signs of cardiac involvement which was diagnosed as a constrictive pericarditis. Roentgen-ray examination of the lungs did not show parenchymatous alterations; nevertheless in the operation a tumor of bronchial origin was found, which was hidden by a shadow of right pleural effusion. In the operation the strong adhesions found between lung and diaphragm prevented the liberation of the heart. Post-mortem examination showed a tumor of the right lung that had invaded secondarily the right and part of the left auricle, which was recognized as an epithelioma of bronchial origin. AUTHOR.

Herztein, J., and Weinroth, L. A.: Arteriosclerotic Peripheral Vascular Disease in Diabetes, Arch. Int. Med. **76:** 34, 1945.

Confirming the work of others, our observations indicate that an apparently selective and frequently premature arteriosclerosis occurs in the peripheral vessels of the lower extremities in diabetic patients.

The increased incidence of arteriosclerosis in diabetic patients, irrespective of the usually accepted factors which determine arteriosclerosis in nondiabetic persons, may indicate a metabolic origin or imply an acceleration of the process by some metabolic factor. From the statistical standpoint of our study, the relationship between such factors and peripheral vascular disease is not made evident.

The presence of cholesterol deposits in the arteriosclerotic lesion and the hypercholesterolemia of patients with neglected or poorly controlled diabetes suggest a linkage between the two disorders. However, no such connection has so far been unequivocally established. It does not, of course, follow that in the treatment of diabetes such factors as control of weight and hypertension can be ignored or that suitable dietary and insulin regimens can be neglected. AUTHORS.

Gregory, R., Ewing, P. L., Levin, W. C., and Ross, G. T.: Studies on Hypertension, Arch. Int. Med. **76:** 11, 1945.

The vasoconstrictor effect of angiotonin can be detected in perfusions of whole pithed frogs.

Angiotonin may be ultrafiltrated and detected in blood plasma ultrafiltrates by this method of bioassay.

Angiotonin may be demonstrated in the ultrafiltrates of plasma from patients whose blood pressures have been elevated by intravenous injections of angiotonin.

Ultrafiltrates of blood plasma from normal and from hypertensive patients contain an almost identical amount of vasoconstrictor substance or substances.

Ultrafiltrates of blood plasma from patients made transiently hypertensive by angiotonin contain a much greater amount of vasoconstrictor substance than ultrafiltrates of plasma from hypertensive patients whose blood pressures are much higher.

Plotted curves of vasoconstrictor effects of ultrafiltrates of plasma from normotensive and from hypertensive persons are identical and differ greatly in character from curves of vasoconstrictor effects of angiotonin in frog Ringer solution or in ultrafiltrates of blood plasma to which angiotonin has been added.

Angiotonin is not present in increased amounts in the blood of patients with essential hypertension of long duration.

In essential hypertension of long duration, the elevation of blood pressure is not due to increased production of angiotonin. Essential hypertension is probably not caused by an increased production of angiotonin. AUTHORS.

Gross, R. E.: Arterial Embolism and Thrombosis in Infancy, Am. J. Dis. Child 70: 61, 1945.

A study was made of forty-seven patients, including six of my own, who had arterial thrombosis or embolism in early life, principally in the neonatal period. The origin of the occlusion was often obscure, but in some cases it was apparently caused by trauma, infection, embolism from aseptic cardiac vegetations or abnormal clotting in the presence of polycythemia. I should particularly like to draw attention to two additional mechanisms whereby arterial vascular accidents can be produced in babies. With the first, the thrombosis of the umbilical arteries extends beyond the expected normal range so that the clot extended into the pelvic arteries or into the lower portion of the aorta. With the second, a closing ductus arteriosus may be the seat of thrombus formation, from which emboli can be thrown off into the pulmonary or the peripheral circuit.

In infants, arterial obstruction was found in the brain, the kidneys, the mesentery, the lungs, the arms, and, especially the legs. The prognosis for many of these subjects is serious: One-half of the patients in the series died. Fatalities which are secondary to cardiac disorders will probably always be unavoidable, but death from secondary sepsis can often be prevented by adequate care of an affected limb, by use of sulfonamide compounds and penicillin, and by amputation when necessary.

It is important to note that ischemia of an extremity does not necessarily mean that the part will die or that early amputation will be required. Occlusion of a large artery may at first seem incompatible with survival of the limb, but experience has shown that the collateral vessels of a baby have an extraordinary capacity for maintaining the blood flow. Hence, amputation should be deferred as long as is expedient; secondary infection should be carefully prevented, and every effort should be made to augment the impaired circulation. If an ischemic limb can be tided over its period of initial insult, there is a fairly good chance that it will survive and will regain satisfactory function. AUTHOR.

Selzer, A.: Circulation in Acute Myocardial Infarction, Arch. Int. Med. 76: 51, 1945.

Forty-five unselected patients with acute myocardial infarction were studied by serial determination of the arm-to-tongue circulation time and twenty-two of them also by serial determinations of vital capacity. The results were correlated with the clinical observations and with the course of the disease.

In all but three patients the initial readings of the circulation time were above normal, the average value for the series being 24.3 seconds (normal 13 seconds). In twenty-four of the thirty-two patients who recovered clinically there was a significant decrease in the circulation time on subsequent readings.

Prolonged circulation time indicating left ventricular failure was found most definitely in patients with clinical evidence of cardiac insufficiency (nineteen patients with an average value of 28 seconds); however, in patients who were entirely asymptomatic except for pain, there was still a definite delay, indicating latent left ventricular failure (twenty-six patients with an average of 21.4 seconds).

Determinations of circulation time are of practical value and are thought to be worth while as a routine procedure in myocardial infarction (a) as an acid in diagnosis by helping to differentiate it from other conditions associated with pain in the chest and (b) in evaluating the progress of circulatory readjustment after an infarction by means of repeated determinations of circulation time. AUTHOR.

Taylor, H. L., Erickson, L., Henschel, A., and Keys, A.: The Effect of Bed Rest on the Blood Volume of Normal Young Men, Am. J. Physiol. 144: 227, 1945.

1. The effect of three weeks of complete bed rest on the blood volume and its component parts has been studied in six experiments on five normal young men. In four men, studies were carried out during the course of reconditioning. In addition, one of these men was studied before and after the surgical repair of an inguinal hernia.

2. An average loss in blood volume of 572 ml., or 9.3 per cent, occurred during the period of bed rest. This was almost entirely accounted for by a contraction of the plasma volume of 518 ml., or 15.5 per cent.

3. The first week of reconditioning resulted in an increase in plasma volume to prebed rest levels but was accompanied by an apparent loss of red cells so that the average increase of blood volume was only 235 ml. The subsequent apparent increase in blood volume to the original level was due entirely to an increase in red blood cells.

4. The blood volume change after the surgical repair of an inguinal hernia and three weeks' bed rest in one man did not differ significantly from the changes observed in the same man after simple bed rest alone.

5. Correlations between blood volume changes and various indices of deterioration of cardiovascular function are discussed. AUTHORS.

Moia, B.: Treatment of Night Cramps and the So-Called Vasomotor Neurosis of the Extremities With Quinine, Rev. argent. de cardiol. 11: 376, 1945.

The syndrome described by Nothnagel as angina pectoris vasomotoria is described showing that it has nothing in common with angina pectoris and that it is only a clinical form of the so-called vasomotor neurosis. Considering the many points of contact between this syndrome and the night cramps of the extremities the author treated it with quinine.

As previously recommended for the latter, the author administered 0.20 Gm. of quinine sulphate per os, at night, before bedtime, to thirty women between 38 and 59 years of age. In all these cases vasodilator drugs and other treatments, including those which improved coexistent hypertrophic arthritis, had been ineffective.

Great improvement was obtained in 70.3 per cent of cases. After withdrawal of the drug, improvement persisted until about twenty days; on recurrence of symptoms the re-administration of quinine was again effective.

The etiopathogenic relations between the vasomotor neurosis of the extremities and the night cramps are discussed as well as the mechanism of action of quinine. AUTHOR.

Holzmann, M., and Spuhler, O.: Infarct Electrocardiogram and Veronal Poisoning, Cardiologia 6: 225, 1942.

In a case of old posterior wall infarct, the appearance of an electrocardiogram of the early stage type was observed during veronal poisoning, without new infarction. This shows that this electrocardiograph type, in the case of localized coronary circulatory disturbance, may be produced not only by overwork by a blood pressure crisis or by an acute ischemia, but also by acute toxic cellular metabolic disturbance. AUTHORS.

Murphy, G. E.: Salicylate and Rheumatic Activity, Bull. Johns Hopkins Hosp. 127: 1, 1945.

An objective study of the clinical course and histologic character of rheumatic lesions in twelve actively rheumatic patients treated with large doses of salicylate was carried out. In six patients the size of involved joints and in six patients size and skin temperature of involved joints were followed by direct measurement in an attempt to determine the effect of salicylate upon the local rheumatic inflammation. The results in this small series of cases do not support the widely accepted view that salicylate promotes the subsidence of the rheumatic joint inflammation. In several of these patients characteristic rheumatic lesions developed in a variety of sites during the course of salicylate therapy. In two cases tendon sheath nodules developed; with another case a tenosynovitis developed with the serum salicyl level between 300 and 450 gammas per cubic centimeter, respectively. In another case the tenosynovitis developed with the serum salicyl level between 350 and 265 gammas per cubic centimeter. A florid rheumatic pneumonitis appeared to develop in a fatal case with the serum salicyl level above 300 gammas per cubic centimeter, another striking finding at autopsy in this case being fresh fibrin thrombi in capillaries of practically every glomerulus in sections of both kidneys. In a fifth patient an episcleral nodule developed with the serum salicyl level between 450 and 600 gammas per cubic centimeter. The histology of these lesions is illustrated and described. A review of the literature pertaining to episcleral and scleral lesions developing in the course of active rheumatic fever and evidence for considering the episcleral lesion in the present studies of rheumatic nature are presented. In a sixth patient joint rheumatic activity became manifest for the first time during the course of heavy salicylate therapy (after fifteen days of large doses of salicylate) associated with electrocardiographic evidence of increased cardiac rheumatic activity. AUTHOR.

Rich, A. R.: Hypersensitivity to Iodine as a Cause of Periarteritis Nodosa, Bull. Johns Hopkins Hosp. 77: 43, 1945.

Previous studies have demonstrated that anaphylactic hypersensitivity to foreign serum and to sulfonamides can cause periarteritis nodosa. The present report adds iodine to the

sensitizing substances that can cause this destructive vascular lesion, and emphasizes that substances of widely different chemical nature have this potentiality, depending upon their ability to induce the state of anaphylactic hypersensitivity. AUTHOR.

Wedd, A. M., and Blair, H. A.: The Effect of Barium Chloride on the Heart, J. Lab. & Clin. Med. 30: 765, 1945.

The effect of barium chloride on the whole auricle and on strips of ventricle of the turtle heart has been studied. The principal action of the drug was to increase rhythmicity. This effect was more marked when the rate of beating was relatively low, and also when the tissue had been removed from the animal for twenty-four or more hours. Contractility was usually depressed. The influence on excitability, measured by the Q-T of the electrogram, and on muscle fiber conduction was slight. AUTHORS.

Steinberg, F., and Jensen, J.: On the Use of Theophylline Aminoisobutanol in Angina Pectoris, J. Lab. & Clin. Med. 30: 769, 1945.

There is no significant absence of attacks of angina pectoris during the periods when the patients received theophylline aminoisobutanol as contracted with the periods when they received the inert substance or no drug at all. It is concluded that theophylline in general, and specifically theophylline aminoisobutanol, exerts no demonstrable effect upon the incidence of attacks in patients with angina pectoris. AUTHORS.

Raab, W.: Diminution of Epinephrine Sensitivity of the Normal Human Heart Through Thiouracil, J. Lab. & Clin. Med. 30: 774, 1945.

Thiouracil administration for three months to ten physically healthy persons was followed by a significant diminution of the sensitivity of the heart to epinephrine (heart rate, electrocardiogram). The behavior of the blood pressure was rather uncharacteristic. Implications of these observations regarding the pathogenesis and treatment of angina pectoris are briefly discussed. AUTHOR.

Guerra, F., and Chavez, N.: Value of Iontophoresis With Sodium Salicylate in Cardiovascular Rheumatism, Arch. Inst. cardiol. México 15: 153, 1945.

Following intravenous injection of 1 Gm. of a 10 per cent sodium salicylate solution per 50 kg. body weight after ten minutes a level of 150 ± 17 micrograms per cubic centimeter of salycilicion in blood serum was obtained.

After ion transfer with 2 to 4 per cent sodium salicylate solution with 5 to 10 milliamperes during fifteen to thirty minutes in the precordial region no traces of salycilieion were present in the blood.

The drug concentrations of the solution before and after the ion transfer were the same.

The claims of clinical improvement is cardiovascular rheumatism following ion transfer with sodium salicylate are, therefore, not due to the presence of the drug in blood or to its specific action upon rheumatism. AUTHORS.

Allmark, M. G., and Bachinski, W. M.: Present Status of the Standardization of Digitalis and Strophanthus Products in Canada, Canad. M. A. J. 53: 361, 1945.

The purpose of this paper from the laboratory of Hygiene, Department of National Health and Welfare, Ottawa, is to present a report on the comparative assays for standardization of digitalis, and to discuss the responsibility of the Department of National Health and Welfare as a regulatory body in connection with standardization of these products in Canada.

Canadian pharmaceutical companies would obtain more uniformity in potency for both digitalis and strophanthus preparations if the U.S.P. XII cat method was employed to standardize their products.

Digitalis products which are not reproducible from batch to batch and from which no national standards are available should be standardized by a biological method, and a standard used which is qualitatively the same as the samples tested.

Preparations like digitalin (crystalline) should not be labeled in International Units. The human requirements of digitalin are considerably less than the potency ratio between digitoxin and digitalis on cats would indicate. MCCULLOCH.

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The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

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